VOLUME 78 • SEPTEMBER 1958 • NUMBER 3

ARCHIVES OF DERMATOLOGY

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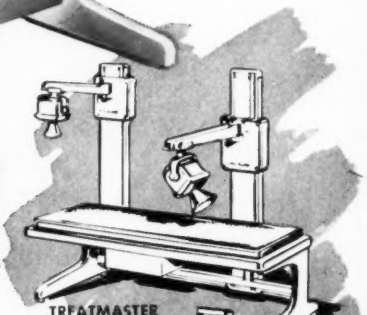

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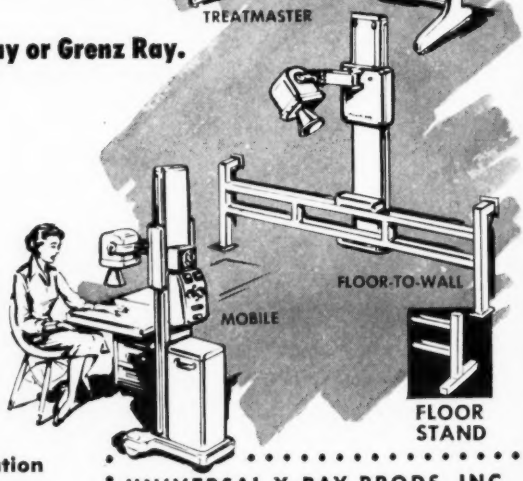

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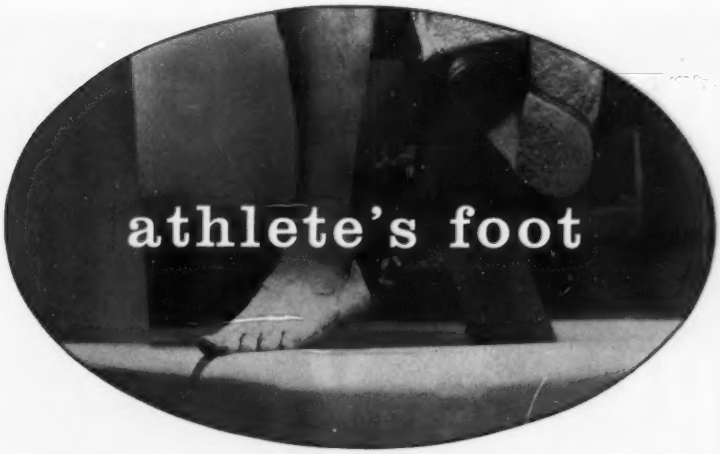

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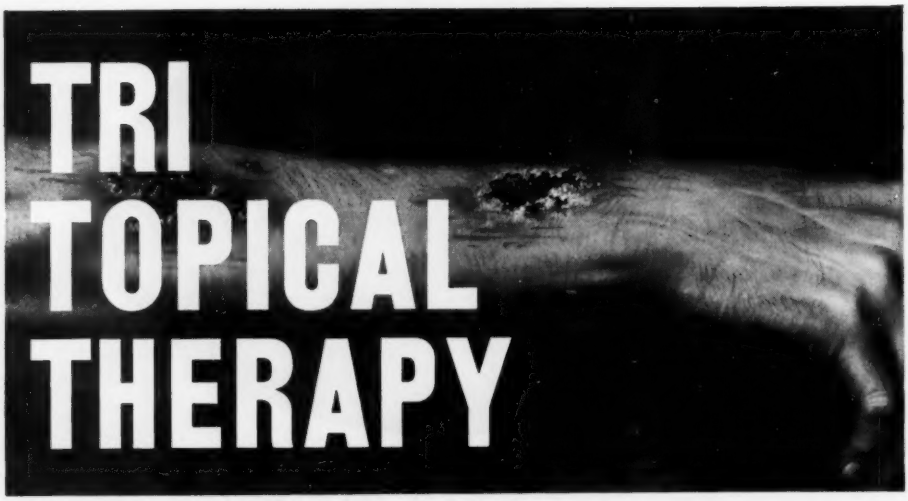

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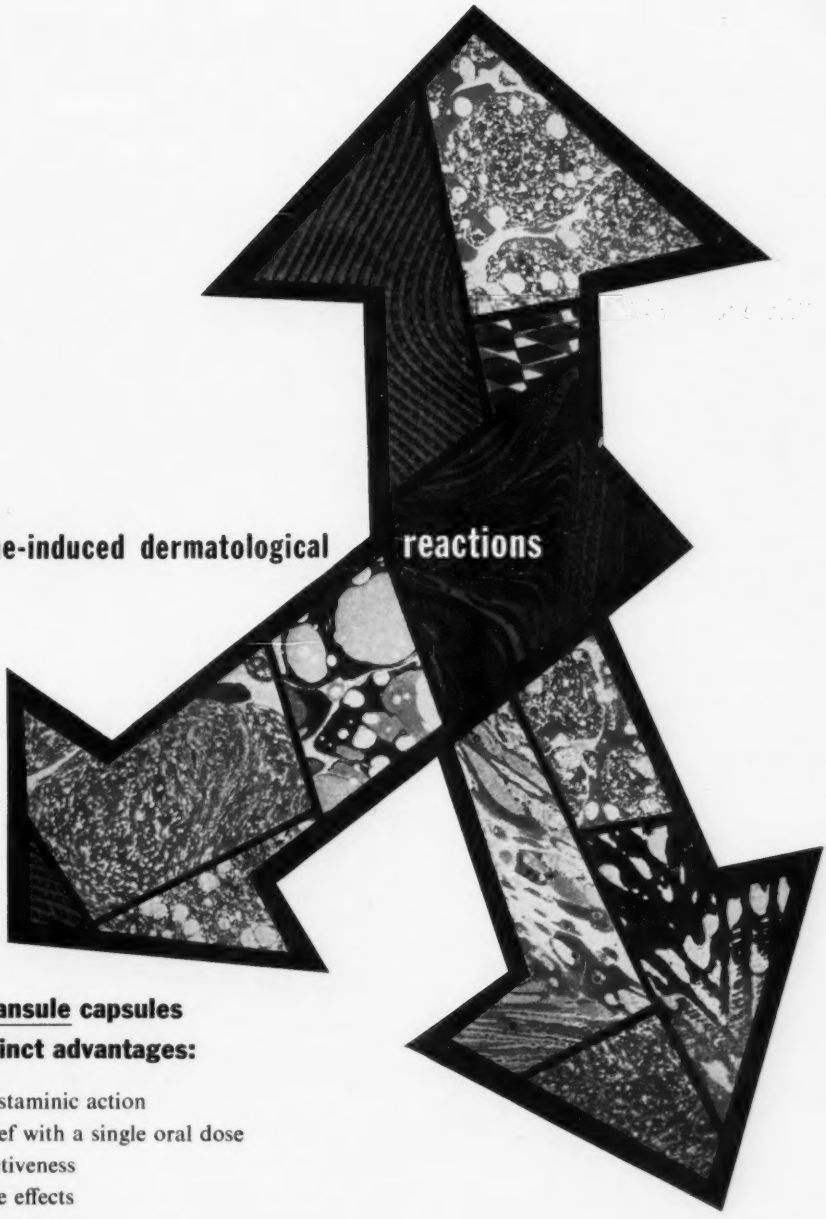

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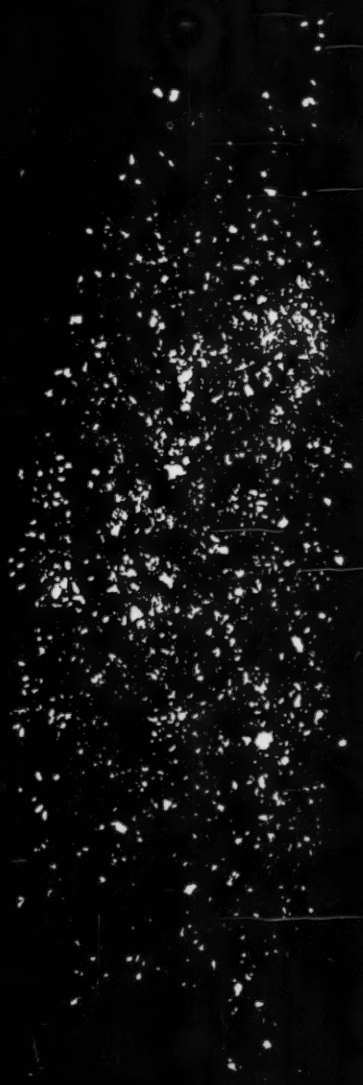

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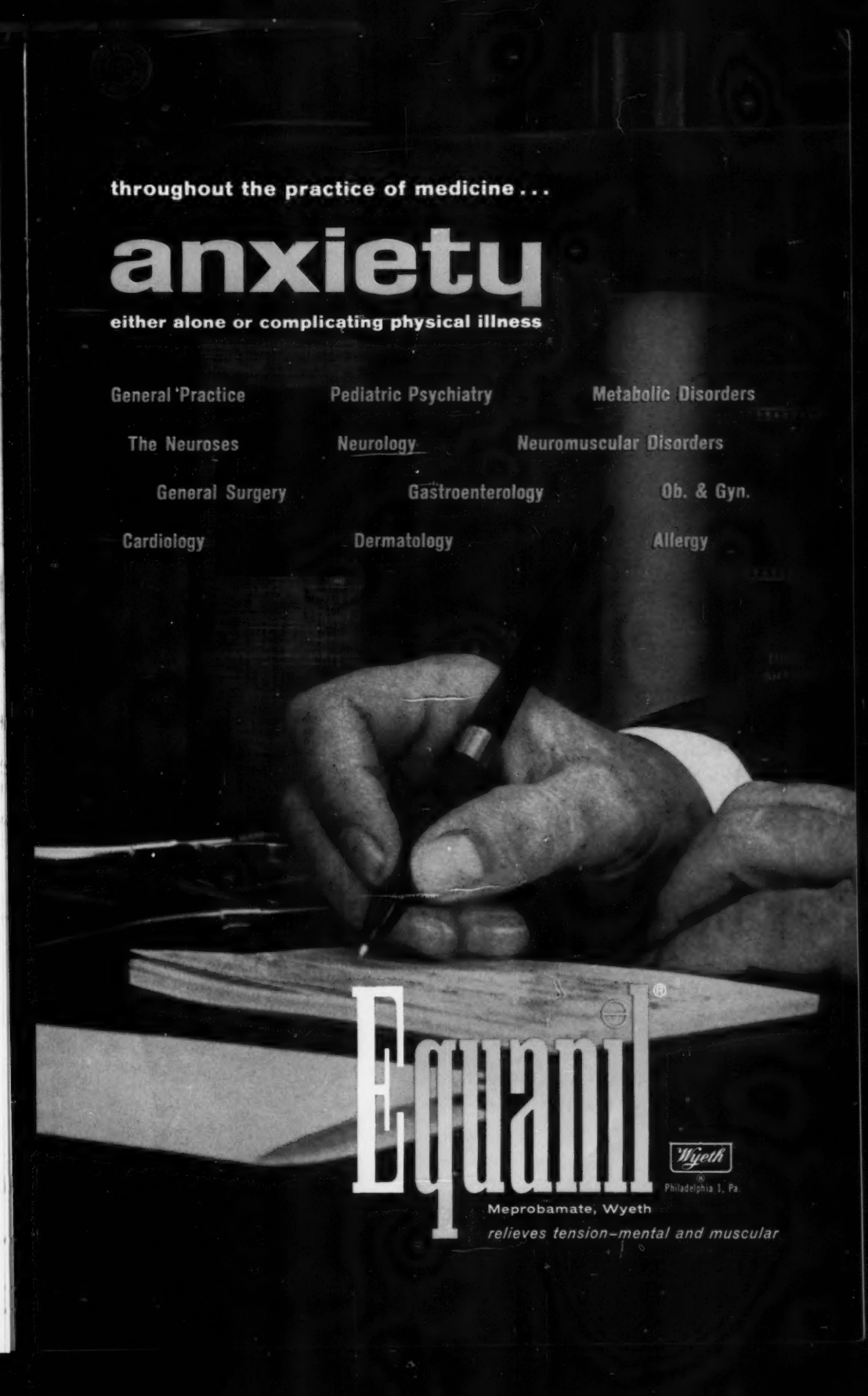
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*Peck, S. M.; Traub, E. F., and Spoor, H. J.: A.M.A. Arch. Dermat. & Syph. 67:263, 1953.

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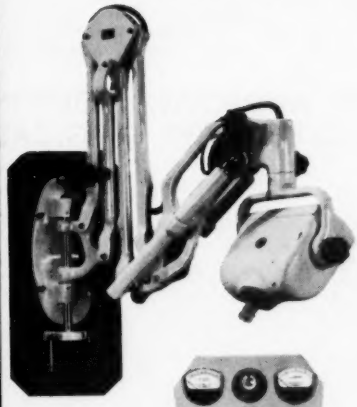

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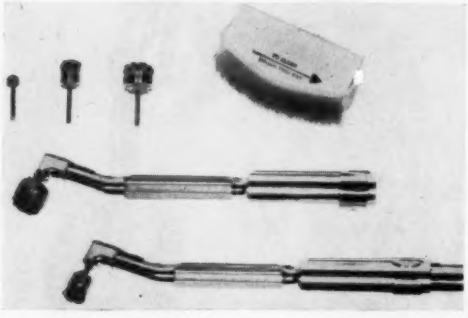

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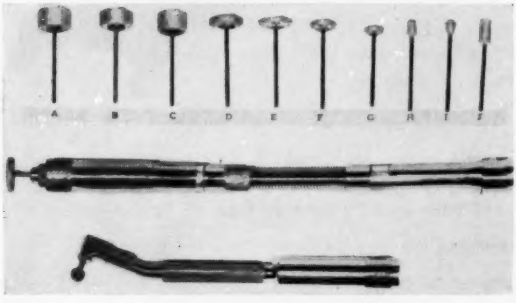

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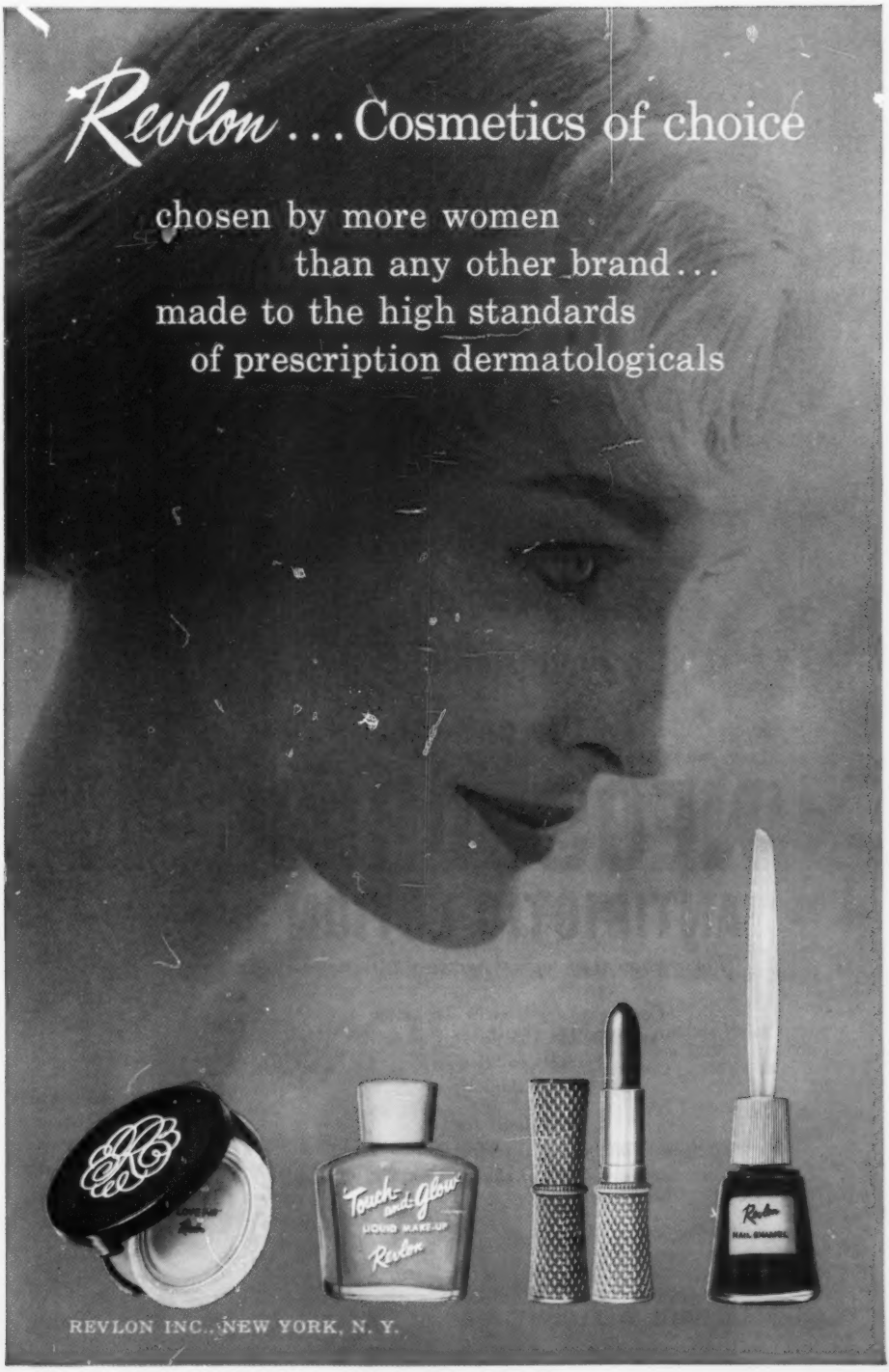
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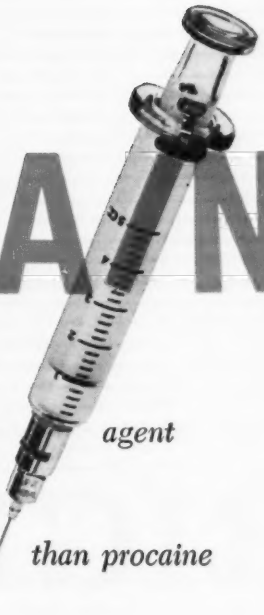

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1. Colavincenzo, J. W., and others: Pennsylvania M. J. 59:338 (March) 1956.
2. Ansbro, F. P., and Furlong, R. E.: Adelphi Hosp. Bull. 15:2 (May) 1957.
3. Foldes, F. F., and McNall, P. G.: Anesthesiology 13:287 (May) 1952.

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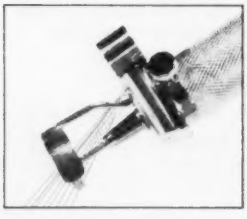

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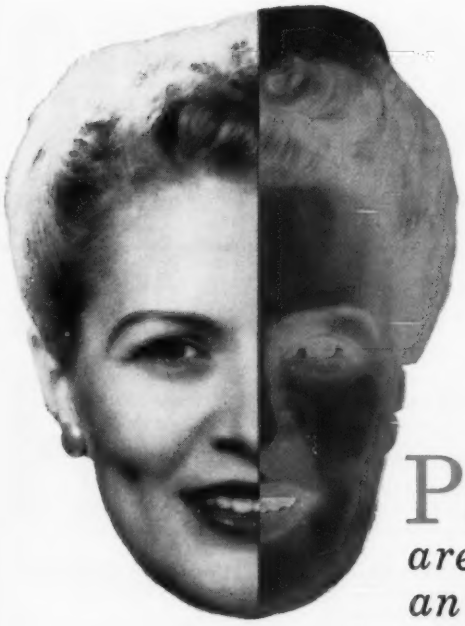

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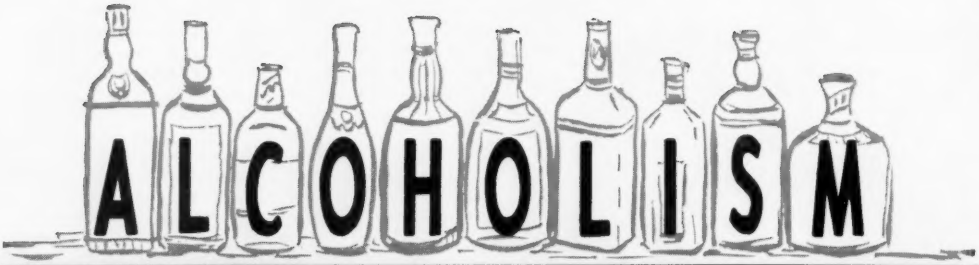

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References: 1. Sokoloff, O. J.: Meprobamate (Miltown) as adjunct in treatment of anogenital pruritus. A.M.A. Arch. Dermat. **74**:393, Oct. 1956. 2. LeVan, P.: Clinical dermatologic studies of four chemically different tranquilizers. Clinical Med. **4**:1089, Sept. 1957.

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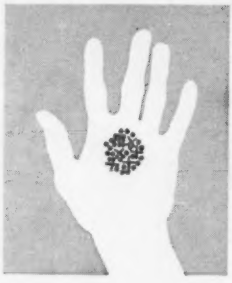

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1. Reports to the Squibb Institute of Medical Research, 1957. 2. Sherwood, H., and Cooke, R. A.: J. Allergy 28:97, 1957. 3. Hellman, L., et al.: American Rheumatism Association. Interim session, Nov. 23, 1956. 4. Berntsen, C. A., Jr., et al.: New York Rheumatism Association. Annual meeting, April 9, 1957, New York. 5. Freyberg, R. H., et al.: International Congress on Rheumatic Diseases, June, 1957, Toronto.

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1. Wiener, K.: Systemic Associations and Treatment of Skin Diseases, St. Louis, The C. V. Mosby Company, 1955, pp. 329; 458-459.
2. Perry, D. J.; Mount, G. D., and Browne, B. W.: The Effect of Varying Oral Dosages of Banthīne, Pro-Banthīne and Prantal on the Galvanic Skin Response, J. Invest. Dermat. *28*:239 (March) 1957.
3. Olansky, S., and Callaway, J. L., in Modern Medicine 1958 Annual (Part 1): Management of Superficial Infections, Minneapolis, Modern Medicine, 1957, p. 46.

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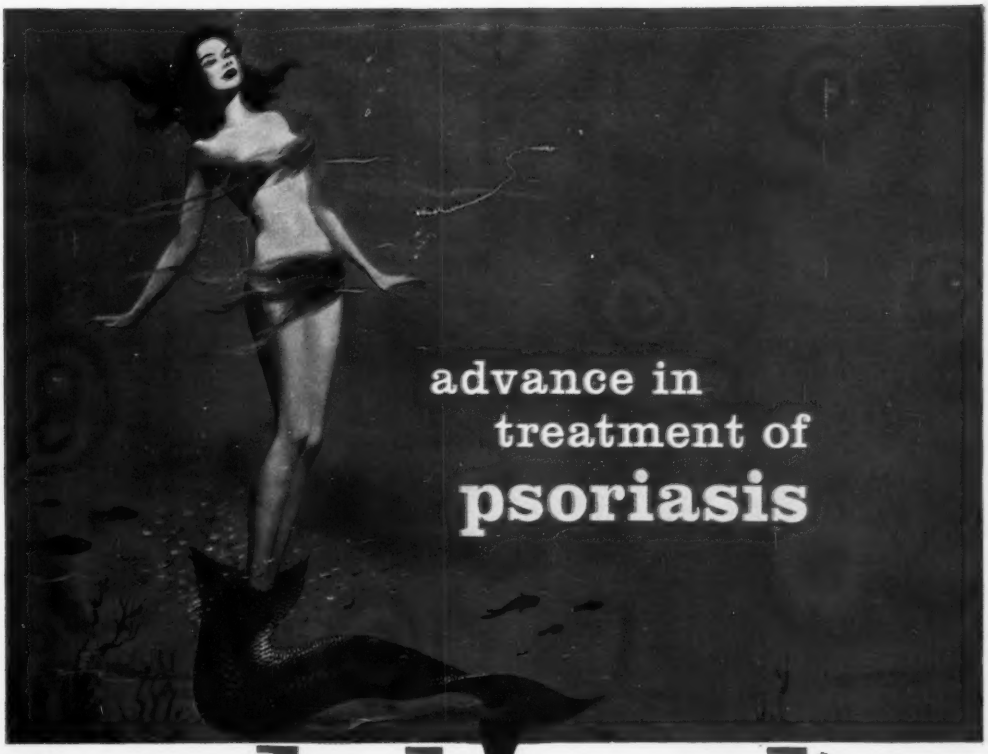

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Supplied: Bottles of 8 fl. oz.

(1) Flesch, P.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). (2) Bleiberg, J., and Saltzman, J. A.: Clin. Med. *5*:485 (Apr.) 1958. (3) Bleiberg, J.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). (4) Clyman, S. G.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). *Trademark

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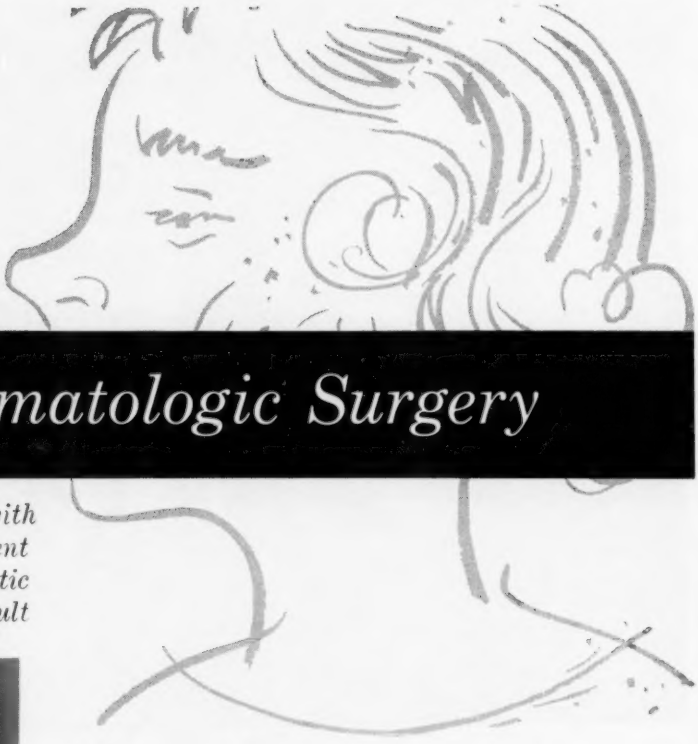

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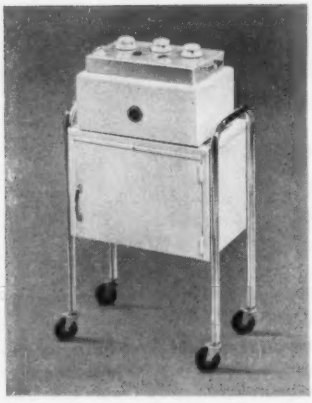

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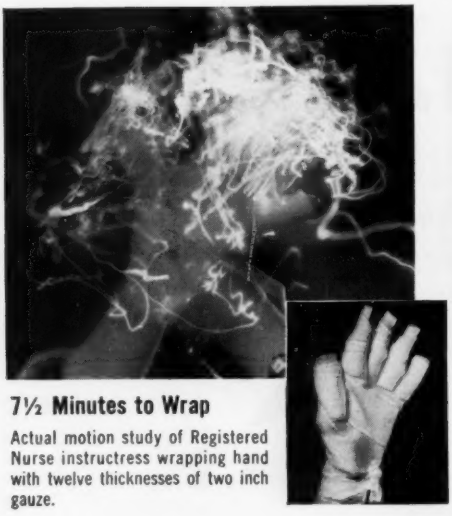

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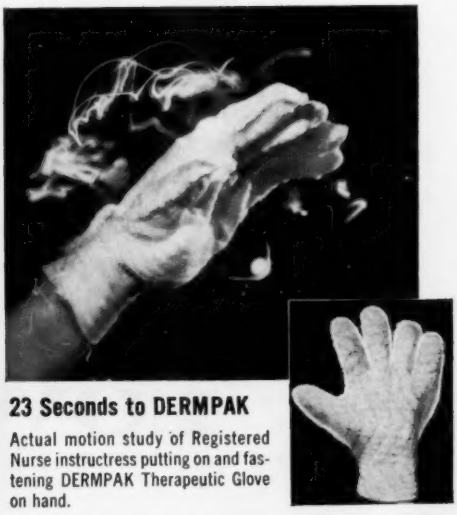

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Acute Peptic Ulcer After Triamcinolone Therapy

Report of Three Cases

CHARLES H. BROWN, M.D., and JOHN R. HASERICK, M.D., Cleveland

Steroids such as corticotropin, cortisone, hydrocortisone, predisone, and prednisolone have become useful therapeutic drugs in a number of conditions. In a small percentage of patients an unfortunate sequela of steroidal therapy has been the development of peptic ulcers, both gastric and duodenal. No matter which cortisone or cortisone-like drug is used, the incidence of ulcer does not seem to vary. In general, peptic ulcer develops more frequently in those patients who have been given large doses of steroids for relatively long periods of time.

It has been our experience that the majority of patients in whom "steroid ulcers" develop previously have had peptic ulcers or have some other contributing condition such as duodenal stasis associated with mesenteric root compression. We, and others, by combining simple ulcer treatment with steroid therapy, have been able to give steroids safely to patients who previously have had peptic ulcers, and those patients have had no recurrence of the ulcers. Peptic ulcers have been healed in patients in whom it was necessary to continue steroid therapy for other serious diseases, such as lymphomas and systemic lupus erythematosus. In some patients there has been no delay in healing of gastric ulcers even though steroid therapy is continued, provided the patients concomitantly follow adequate ulcer treatment.

The role of steroids in the pathogenesis of peptic ulcers is not clear. Gray, Ramsey, and Thorn [1] have reported an increase in the secretion of hydrochloric acid and pepsin in the stomach and in the excretion of uropepsin in the urine, both after the administration of steroids and in patients with steroid-induced ulcers. Others have not entirely substantiated these findings: Hirschowitz and associates [2] reported a decrease in secretion of gastric mucus, which acts as a protection to the gastric mucosa, after the administration of steroids. A third factor could be the relation between the sodium ion concentration and the secretion of hydrochloric acid.

Seelig [3] has reported that, with triamcinolone,* "Epigastric distress and peptic ulceration must still be guarded against, although their incidence seems to be significantly lower than with the other steroids." No peptic ulcers developed in 28 patients [4] with disseminated lupus erythematosus who were treated with doses of from 20 to 64 mg. daily for as long as eight or nine months. Peptic ulcer developed in only 1 patient of 400 patients [5] given lower dosages of triamcinolone for bronchial asthma and dermatologic conditions. Because of

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From the Departments of Gastroenterology and Dermatology, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute.

* Aristocort, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

these preliminary reports of a low incidence of peptic ulcer in patients receiving triamcinolone, we believe that this report of a patient, in whom an acute duodenal ulcer developed after he had taken small doses of triamcinolone for only two and one-half weeks, and reports of two other cases of ulcer associated with triamcinolone therapy, merit attention.

Report of Cases

CASE 1.—A 41-year-old man who was first examined at the Cleveland Clinic in 1953 had had psoriasis since 1946. He had no gastrointestinal symptoms and no history of any digestive or ulcer symptoms.

On physical examination, dry disseminated areas of erythema covered with scales were present on the scalp, forearms, hands, knees, feet, and genitalia. The fingernails were irregular, with horizontal striae and a few pinpoint holes. Laboratory findings were negative.

The patient was admitted to the Cleveland Clinic Hospital on May 12, 1953, and was given typhoid vaccine intravenously and started on the Goeckerman regimen. He was discharged on May 23, and when he was seen next, on June 2, 1953, the psoriasis was much improved.

Four and one-half years later (Jan. 21, 1958) he returned because of an acute flare-up of the psoriasis. He still had no digestive troubles or symptoms of ulcer. An erythematous lesion without scales was present on the right upper eyelid, and erythematous lesions with scales were present on the elbows, wrists, palms, soles, knees, neck, and anogenital area. The patient was given 16 mg. of triamcinolone daily. The lesions showed some improvement one week later (Jan. 28), and two weeks later (Feb. 4) the psoriasis was 50% better; the dose of triamcinolone was reduced to 12 mg. daily.

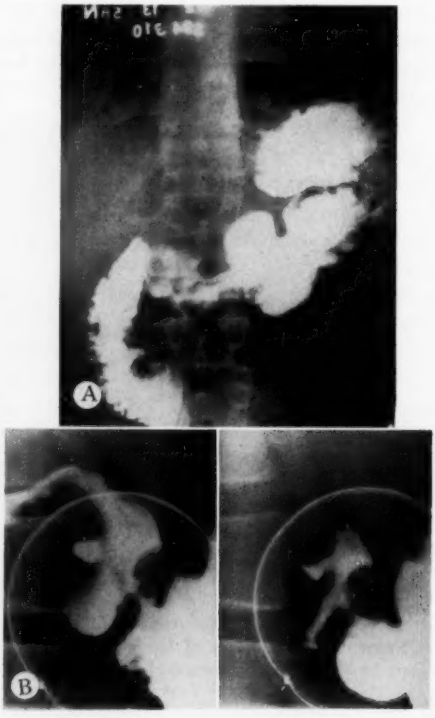
On Feb. 12 (21 days after the triamcinolone therapy was started) further improvement in the psoriasis was noted, the palmar lesions having disappeared. However, the patient reported that he had passed two tarry stools and that he had had intermittent, recurrent epigastric pain lasting one-half hour at a time for the past several days. He had taken no medications or antacids for the pain. He was admitted to the hospital for diagnosis and treatment.

On physical examination, the pulse rate was 80, temperature 98.4 F, and blood pressure 130/85 mm. Hg. The psoriatic lesions were as previously noted. Palpation of the abdomen disclosed localized tenderness that was restricted to a small area in the epigastrium and the right upper quadrant. No masses were palpated, and there was no muscle spasm. The other physical findings, including those of the heart, lungs, and rectum, were normal.

Laboratory Findings.—Hemoglobin was 14.1 gm. per 100 mg. (normal in our laboratory is 16.5 gm.). Subsequent determinations of the hemoglobin showed no change. The leukocyte count was 8650 per cubic millimeter. Urinalysis and Wassermann and Kahn tests were negative. Fasting blood sugar was 76 mg. per 100 ml. Two stool specimens were positive for occult blood (Guaiac). Gastric analysis, after betazole hydrochloride (Histalog) was used as a stimulant, showed marked hyperacidity, the free hydrochloric acid being 130 units and the total acidity being 140 units.

Roentgen Findings.—Chest and kidney-ureter-bladder roentgenograms were negative, with no evidence of free air under the diaphragm. Roentgenograms after barium swallow showed the esophagus and the stomach to be normal. There was minimal deformity of the duodenal bulb, and

Roentgenogram of the stomach (Feb. 13, 1958). *A*, survey film after barium swallow. The stomach is normal, but there is a large ulcer crater indicated in an undeformed duodenal bulb. *B*, spot film showing a large ulcer crater in the undeformed duodenal bulb.



a large ulcer crater on the posterior wall of the bulb was demonstrated (Figure).

Treatment and Course.—Treatment consisted of a bland diet with food or milk on the even hours, antacids on the odd hours, mild sedation, and an anticholinergic drug four times daily.[6] The patient was asked to discontinue taking the triamcinolone. The epigastric pain promptly disappeared within 24 hours, despite the fact that the patient, unknown to us, surreptitiously continued to take 8 mg. of triamcinolone daily for one week. After we again insisted that he stop the steroid medication, he avoided any further use of the drug.

The patient remained free of epigastric pain and was discharged on Feb. 21, 1958. He was asked to continue his strict ulcer program. Topical medication was prescribed: 0.25% anthralin ointment twice daily for all psoriatic lesions and iproniazid ointment for the fingertips.

When examined one week later (Feb. 28), the patient had adhered carefully to his ulcer program and had been entirely free of any ulcer symptoms. The psoriatic lesions were slowly recurring.

On April 1 the patient reported that he had had no ulcer symptoms since beginning the ulcer treatment. Hemoglobin was 16.3 gm. Roentgen examination of the stomach showed no evidence of the ulcer crater demonstrated previously. The psoriasis was worse. Ulcer therapy is being continued, and the patient is being given triamcinolone, 8 mg. daily.

CASE 2.—A 50-year-old woman had severe rheumatoid arthritis for 11 years, since 1947; she had been receiving some type of steroidal therapy for the last five years. Her local physician prescribed triamcinolone on March 1, 1958, in a dosage of 16 mg. daily. Six weeks after the triamcinolone therapy was started, intermittent episodes of severe epigastric pain occurred, followed by vomiting. We first examined the patient on May 1, at which time she was hospitalized for diagnosis and treatment. On gastric analysis after administration of betazole hydrochloride (Histalog) there were 34 units of free and 54 units of total HCl. Roentgen examination of the stomach disclosed a small ulcer crater projecting from the lesser curvature of the gastric antrum. She was given a course of intensive ulcer therapy: food or milk on the even hours and antacids on the odd hours. Twelve days later (May 17), roentgen examination disclosed the ulcer crater still to be present but smaller. The patient was discharged from the hospital but was advised to continue with the ulcer program; the dosage of the steroid was reduced and changed to 10 mg. of cortisone twice daily for the rheumatoid arthritis. Of clinical interest is the fact that this patient took steroids for five years and no ulcer occurred, roentgen findings of the stomach two years previously being normal. Yet, after she had taken moderately large doses of triamcinolone (16 mg. daily), a gastric ulcer developed.

CASE 3.—This case of ulcer occurring after triamcinolone therapy was reported to us by the local physician of the patient. We had seen the patient several years previously for psoriasis, at which time no ulcer was present. Her local physician recently prescribed triamcinolone for her psoriasis, and after six weeks of therapy an acute duodenal ulcer developed.

Comment

Case one is of interest because symptoms of ulcer developed in the patient within a short time after steroid (triamcinolone) therapy was started for psoriasis. Two and one-half weeks after starting to take triamcinolone (16 mg. daily for two weeks and then 12 mg. daily), this patient, having had no antecedent ulcer, passed two tarry stools and had epigastric pain. A large duodenal ulcer was roentgenographically demonstrated. The symptoms of ulcer promptly disappeared after ulcer therapy was begun, although the patient, against orders, continued taking 8 mg. of triamcinolone daily for one week. The development of an ulcer in such a short time with small doses of the drug suggests that in this patient the steroid may have been ulcerogenic.

The findings suggest that the same precautions concerning ulcer should be taken with triamcinolone as with other steroids. Any patient who has had an ulcer should be following at least a simple ulcer program while taking any steroid therapy. Many patients with steroid ulcers do not have the classic symptoms of peptic ulcer but have the symptoms of the complications of the ulcer, such as massive bleeding and/or perforation. The clinician should constantly be aware of the possibility of the presence of a peptic ulcer that is symptomatically atypical in any patient receiving steroid therapy, including triamcinolone.

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A Nonacantholytic Bullous Dermatosis Associated with Multiple Myeloma

FREDERICK A. J. KINGERY, M.D., and LEOPOLDO F. MONTES, M.D., Ann Arbor, Mich.

Considerable interest in the pemphigoid dermatoses has arisen since Lever [1] demonstrated that these disorders can be differentiated from true pemphigus by the lack of acantholysis in the former and its presence in the latter. It is often difficult, if not impossible, to distinguish among the nonacantholytic bullous diseases which resemble pemphigus vulgaris clinically (dermatitis herpetiformis, erythema multiforme, and bullous pemphigoid). Diagnosis, therefore, is often made on the basis of clinical course, response to therapy, or predominance of a particular feature of one disease.

Eruptions which fall into this group have been reported occasionally in connection with various internal malignancies. The pathogenesis has been thought to be an ill-defined toxic effect of the neoplasm, the lesions usually developing after the appearance of the neoplasm. Cancer of the stomach and metastatic adenocarcinoma of the adrenals or lung have been associated with erythema multiforme [2]; it is also not an uncommon development following irradiation of various other tumors. Dermatitis herpetiformis has been observed in patients with carcinoma of the ovary, thyroid, uterus, vulva, cervix, pancreas, and stomach, as well as with the lymphoblastomas.[2]

The relatively uncommon cutaneous manifestations of multiple myeloma have been thoroughly summarized by Bluefarb.[3] He divides the nonspecific dermatoses into four groups: those due to abnormal proteins, those as a result of pancytopenia, toxic cutaneous lesions, and cutaneous manifestations due to myelomatous involvement of internal organs. No mention is made of an erythema multiforme or pemphigoid response. Andrews,[4] in his discussion of Bluefarb's paper, mentions a case in which a bullous eruption thought to be a generalized herpes zoster occurred in a person with multiple myeloma. Brauman et al.[5] in Belgium recently reported a case of myeloma with unusual cutaneous manifestations, characterized in part by subepithelial bulla formation discovered on histological examination.

Substantially complicating the situation is the fact that there is adequate experimental and clinical evidence [5-8] to suggest that hyperglobulinemia and plasmacytosis can develop on the basis of hypersensitivity, producing a picture not unlike multiple myeloma. It is well known that erythema multiforme bullosum can occur as a result of drug hypersensitivity, notable among such drugs being the sulfonamides. There are several cases on record [6,7] of hypersensitivity to sulfonamides which resulted in plasmacytosis and hyperglobulinemia. The following case is of particular interest in this regard.

Report of a Case

The patient, a 58-year-old white male steelworker, first noticed a burning sensation and blister formation on the thighs while hunting, in November, 1956. Similar lesions subsequently appeared over both legs and forearms, although there were no palmar, plantar, or oral lesions. For a three-month period he was given corticosteroids and sulfapyridine by his local physician, without appreciable change. The patient stated he had taken no sulfonamides or other medications immediately prior to onset of the eruption, and he

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From the Department of Dermatology, University of Michigan Medical School.

Fig. 1.—Flaccid irregular bulla on the right thigh.

was uncertain about the possibility of having received sulfonamides in the past. He was first seen at the University Hospital, University of Michigan, on March 13, 1957, at which time there were scattered fragile intact bullae (Figs. 1 and 2) on all extremities and a markedly positive Nikolsky sign. Biopsy of a fresh lesion (Fig. 3) revealed a subepidermal bulla without evidence of acantholysis, consistent with a diagnosis of erythema multiforme, dermatitis herpetiformis, or so-called "bullous pemphigoid." He was given prednisolone, 30 mg. per day, for one week and then 45 mg. per day when no response was obtained.

First Admission (March 17, 1957, to March 29, 1957).—The patient was hospitalized for further study. On admission his weight was 236 lb. and physical examination was within normal limits except for the persistent cutaneous lesions.

Laboratory examinations showed Hemogram, normal; urinalysis, persistent 2+ to 3+ albuminuria; nonprotein nitrogen, 50 mg. %; phenolsulfonphthalein test and creatinine clearance, normal. Chest x-ray and Kahn serologic reactions were negative. Prednisolone dosage was increased to 80 mg. per day, and sulfapyridine, 1 gm. q. i. d., was added to the regimen. Since there was no evidence of new bulla formation, he was discharged with instructions to decrease the prednisolone gradually while continuing the sulfapyridine. He soon developed new lesions in spite of both of these drugs.

Fig. 2.—Ruptured and flaccid bullae over both thighs and knees. Symmetry is apparent.

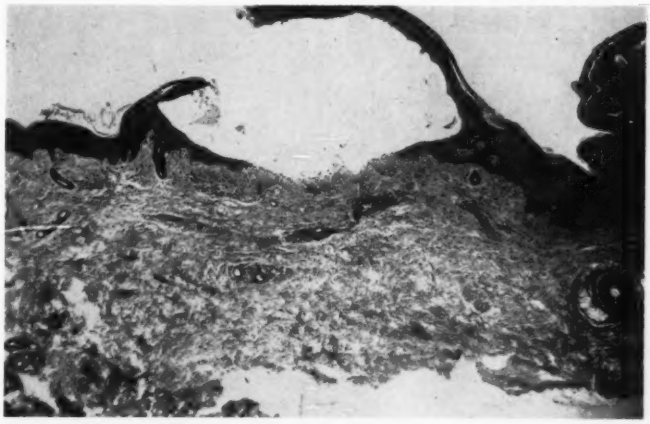


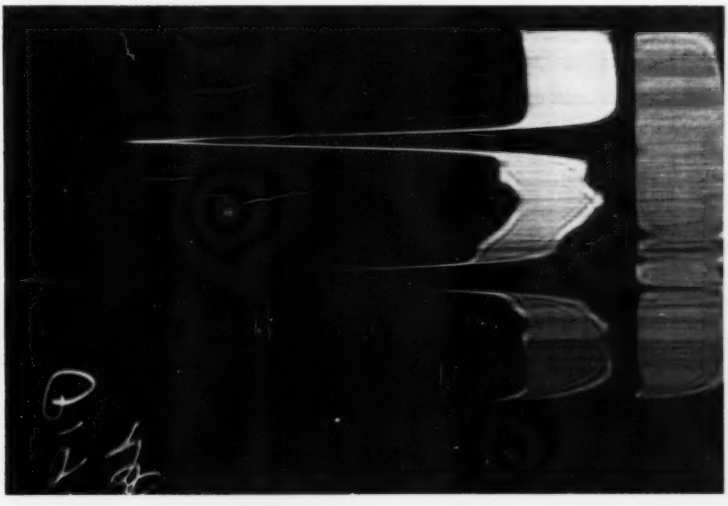
Fig. 3.—Subepidermal bulla; no eosinophils or acantholytic cells were present in the bulla; patchy infiltrate of mononuclear cells around the vessels adjacent to the bulla; × 50.

Second Admission (April 23, 1957, to May 9, 1957).—Sulfapyridine was discontinued shortly after admission because of gastric distress, and the patient was again given 80 mg. of prednisolone and 20 mg. of repository corticotropin injection (corticotropin [ACTH] gel) daily, this time with no improvement. New lesions continued to form on the trunk as well as on the extremities, and marked pigmentation occurred at the sites of previous bullae. A diagnosis of atypical dermatitis herpetiformis was entertained. Other than persistent albuminuria, the routine laboratory studies were still within normal limits. Therapy with sulfoxone (Diasone) was started (0.33 gm. per day) in place of the sulfapyridine, and he was discharged.

Third Admission (May 26, 1957 to June 28, 1957).—Seventeen days later the patient returned with extension of his cutaneous disease. He now complained of extreme weakness and fatigability. Physical examination showed many new bullae arising out of apparently normal skin, a positive Nikolsky sign, conjunctival pallor, and a weight of 220 lb.

Laboratory examinations showed RBC, 2,700,000 per cubic millimeter; hemoglobin, 9.2 gm/100 cc.; erythrocyte sedimentation rate, 26 mm. in an hour; WBC, 6050 per cubic millimeter, with a normal differential count. Urine showed 3+ albuminuria; Bence Jones protein test was negative. Free-moving-boundary electrophoresis of serum pro-

Fig. 4.—Free-moving-boundary electrophoresis of serum (ascending curve). Note the high pointed β-globulin peak.



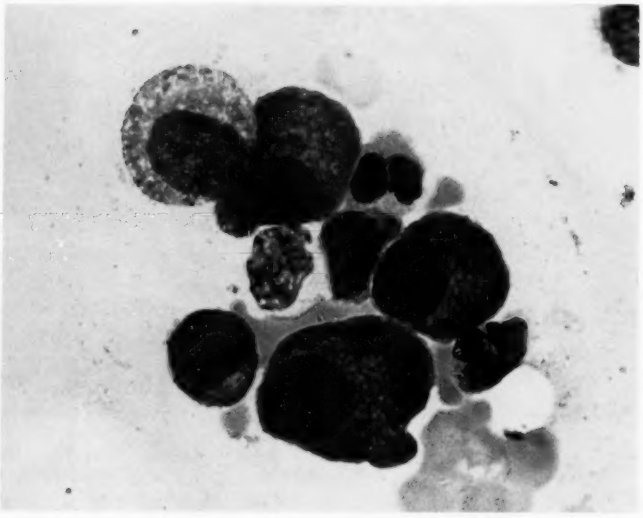


Fig. 5.—Bone marrow smear; plasma cells, showing abnormal cytoplasm; × 1090.

teins (Fig. 4) showed a markedly elevated β-globulin:

	gm. %	%
Total protein	8.29	100.1
Albumin	2.78	33.59
Globulin	5.51	66.42
α_1	0.37	4.43
α_2	0.72	8.70
β_1	4.20	50.69
β_2	0.09	1.07
γ	0.13	1.53
Albumin-globulin ratio	0.51	

The patient was studied by a consultant hematologist. Findings in the bone marrow as well as the clinical picture and other laboratory tests were compatible with a diagnosis of multiple myeloma. Traces of cryoglobulins were present in the serum, and bone marrow studies revealed large numbers of plasma cells showing abnormal cytoplasm (Fig. 5) and some with multiple nuclei (Fig. 6). Complete radiological bone study demonstrated no myelomatous lesion.

On June 11, 1957, urethane therapy was instituted (dosage 0.9 gm. to 2.7 gm. daily), but this

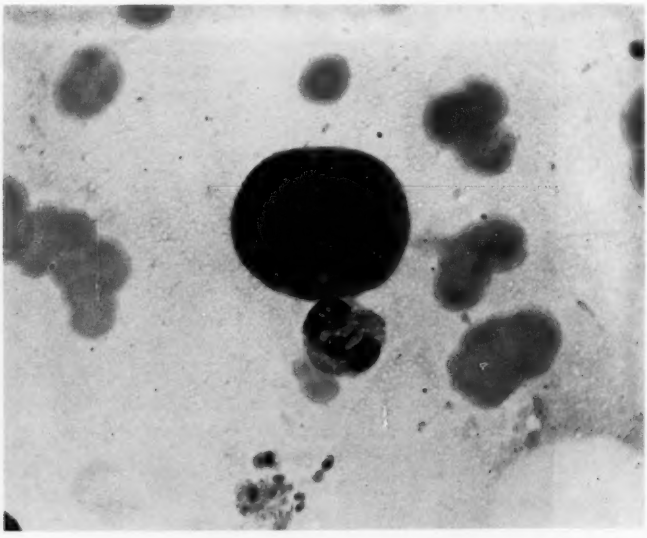


Fig. 6.—Bone marrow smear, showing a plasma cell with two nuclei; × 1080.

was tolerated only a short time because of gastric irritation, although a rise in hemoglobin was noted during this time. From July to October, 1957, the patient was treated again with moderate doses of prednisone by his local physician, with little change in his condition.

Final Admission (Oct. 22, 1957 to Dec. 6, 1957).—This admission was precipitated by increasing weakness and shortness of breath. Findings were essentially as before, except that the patient looked extremely chronically ill. Weight was 190 lb. (representing a 47 lb. weight loss). The liver was palpated 4 fingerbreadths below the costal margin.

Laboratory examinations showed hemoglobin, 8.5 gm/100 cc.; RBC, 2,700,000 per cubic millimeter; WBC, 3150 per cubic millimeter; nonprotein nitrogen, 60 mg. %. Urinalysis consistently demonstrated 3+ to 4+ albuminuria with hyaline and granular casts and many pus cells and erythrocytes. A Congo red test showed that 45% of the dye was removed from the serum.

Urethane was reinstituted, and multiple transfusions were given, but the course was steadily downhill. The nonprotein nitrogen rose to 178 mg. %, the patient developed secondary infections of the gluteal regions and oral mucous membranes, and he died during a convulsive seizure on Dec. 6, 1957. His terminal course was one of progressive renal failure.

On postmortem examination there was plasmocytic infiltration of the liver and mediastinal lymph nodes. Abnormal plasmocytes were abundant in a smear of decalcified bone, although no localized lesions were demonstrated. The kidneys showed extensive changes compatible with a diagnosis of chronic pyelonephritis. The typical "myeloma kidney" was not present.

Comment

The above report describes the seemingly spontaneous appearance of a bullous eruption, unassociated with known internal disease or drug ingestion, followed in a few months by a progressive downhill course terminating in uremia and death. Findings fully compatible with the diagnosis of multiple myeloma were present during life and at postmortem examination, although no discrete osseous lesions were found. The cutaneous part of this patient's disease was thought at different times to be dermatitis herpetiformis, erythema multiforme, pemphigoid, and pemphigus vulgaris. Although the patient received sulfapyridine without effect over extended periods of time during the course of his disease, he denied receiving any similar medication prior to onset of the bullous eruption.

Renal changes were present at the time of the patient's first admission, as evidenced by the significant albuminuria at that time. One must therefore assume that the underlying disease process, asymptomatic as it was, certainly existed at or shortly after the onset of the bullous dermatosis. In the absence of evidence that any drug, notably a sulfonamide, had been administered prior to onset, it would be logical to ascribe these changes to the demonstrated myelomatous infiltration. This evidence would strongly suggest that the pemphigoid eruption in this case is a nonspecific cutaneous response to multiple myeloma.

Multiple myeloma can be divided into four types by electrophoresis of serum proteins: the α-globulin; β-globulin, as in the present patient (Fig. 4); γ-globulin, and pseudo-normal types, with specific elevations in the corresponding protein fractions. In frequency of occurrence these types are as follows:[9]

	%
Pseudonormal	22
α-globulin	6.6
β-globulin	15.4
γ-globulin	54.9

It is interesting to speculate on the similarities between the case under discussion and those reported by Robertson[7] and Wolf and Worken,[6] in which the picture of drug eruption, plasmocytosis, hyperglobulinemia, and progressive anemia developed after the administration of sulfonamides. In our case the eruption preceded the use of sulfonamides, and the presence of not only increased numbers of plasma cells but also marked atypicality of some of the cells led hematological consultants to believe that the patient had true multiple myeloma. Had the patient been receiving sulfonamides at the time of onset one would have had difficulty deciding on the true etiology involved. In any event the similarity is

so striking that it merits more than passing attention, since uncommon reports of this type of response may hold information concerning the possible role played by the sulfonamides in the pathogenesis of certain diseases of grave prognostic implications.

Summary

A case of multiple myeloma heralded by a nonacantholytic bullous eruption is described, in which the eruption appears to be a nonspecific manifestation of the primary disease.

Attention is drawn to the fact that several similar instances of drug eruption, plasmacytosis, hyperglobulinemia, and progressive anemia have occurred after the administration of sulfonamides.

Drs. Norma Blumenfeld, Herbert Spencer, and Ronald Bishop, of the Simpson Memorial Institute, assisted in the hematologic studies.

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Cutaneous Reactions Due to Sulfamethoxypyridazine

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Prlina et al.[1] and Grieble and Jackson[2] have reported on the clinical effectiveness of sulfamethoxypyridazine * (SMPZ) as an antibacterial agent in the treatment of urinary tract infections. Nichols et al.[3], Foerster et al.,[4] and Boger et al.[5] have investigated the pharmacology of this drug. SMPZ was considered useful because a single daily oral dose of 0.5 gm. produced and maintained effective antibiotic concentrations of free sulfonamide in the serum and urine against Escherichia coli. It was readily absorbed from the gastrointestinal tract and slowly excreted in the urine. It was found to have a low degree of acetylation and was more soluble in acid mediums than other sulfonamides. Its antibacterial effectiveness was found comparable to that of sulfadiazine. SMPZ shows some promise in the treatment of dermatitis herpetiformis.[6]

We wish to report the occurrence of erythematous maculopapular dermatitis in patients taking SMPZ. In one patient this progressed to severe generalized dermatitis, while the mild eruptions all cleared promptly on discontinuance of the drug. Two groups of patients receiving SMPZ were observed. One group consisted of 55 patients hospitalized on a genitourinary ward at this hospital. The other group consisted of 30 patients seen in the private practice of a urologist.† In the first group, six reactions were observed; in the second group, seven reactions were noted, making a percentage incidence of 15.3.

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* Kynex, supplied by Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y., for investigational purposes.

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Hospitalized Patients

The hospitalized patients were observed closely for evidence of toxicity. Serum SMPZ levels did not appear to correlate with the incidence or severity of the untoward reactions. Relation to the oral dose was not always evident. However, the patient with the very severe reaction was one of the two reactors receiving the largest total oral dosage.

Some inconsistent variations in the platelet counts of some patients,[1] fever, and dermatitis were the only untoward reactions observed. Of the six patients with untoward reactions to SMPZ (Table 1), two gave a history of previous intake of other sulfonamides. Of the 41 patients who did not react, 14 had previously taken other sulfonamides. Of the seven patients reacting to SMPZ, none had a history of previous allergic reaction, including drug reactions, eczema, hay fever, and urticaria. Of the 41 patients who did not react unfavorably to SMPZ, 6 gave a history of some previous manifestation of allergic reaction, 3 of which were to drugs.

CASE 1.—A 68-year-old white man was hospitalized on the urology ward for transurethral prostatectomy because of benign prostatic hypertrophy. He had an uneventful postoperative course. On the fifth postoperative day he was given 2 gm. of SMPZ, followed by 1 gm. daily. On the day before SMPZ therapy was started, the white blood cell count was 7700, with 56% neutrophils, 30% lymphocytes, 8% monocytes, and 6% eosinophils; hemoglobin was 13.3 gm. %; sedimentation rate, platelet count, hematocrit value, blood urea

TABLE 1.—*Reactors in Inpatient Series*

Case No.	Previous Sulfonamides	SMPZ Dose, Gm.		Total Dose, Gm.	Time of Onset, Day	Symptoms	Time to Clear After Drug Stopped
		Daily	Initial				
2	Yes	0.5	1.5	2.5	2	Dermatitis	3 days
3	No	0.5	1.5	3.5	4	Dermatitis	14 days
4	No	1.0	2.0	4	3	Dermatitis	14 days
1	No	1.0	2.0	15	13	Dermatitis, severely bullous	8 wk.
5	Yes	1.0	2.0	9	7	Urticaria	24 hr.
6	No	1.0	2.0	10	9	Dermatitis	2 days

nitrogen, and liver-function tests were within normal limits.

On the 14th day of therapy he developed conjunctivitis, perioral macular erythema, and fine erythematous papular dermatitis on the chest and neck. SMPZ was discontinued. On the following day the dermatitis became confluent on the chest and appeared on the thighs and upper arms. The patient complained that his soles were tender. Two days later the dermatitis was more widespread and the patient developed edema of the eyelids and serous crusting at the mucocutaneous junctions of the eyelids, nose, and mouth (Figure). Twenty units of corticotropin (ACTH) were given intramuscularly, once daily. Two days later he was lethargic and complained of joint pains and his 24-hour fluid output has dropped to 625 cc. By April 9, 1957, six days after the onset of dermatitis, severe involvement of the mucous membranes of the nose, throat, and eyes was noted. Large bullous and purpuric lesions had developed, and he appeared moribund. He was given 100 mg. of hydrocortisone sodium succinate (Solu-Cortef) intravenously, plus 50 mg. of the same drug, intramuscularly, every six hours. He was given penicillin and streptomycin as well as 15 units of corticotropin in 1000 cc. of intravenous fluid every 12 hours. For six to eight hours there was little response. After 16 hours of such therapy the blood pressure and fluid output had returned to normal and he was more alert.

On April 9, 1957, at the height of his reaction, the white blood cell count was 4950, with 68% polymorphonuclear leukocytes, 28% lymphocytes, 4% monocytes, and no eosinophils. The hemoglobin was 10.8 gm. %. Of the neutrophils, 34 were stab forms and 2 were metamyelocytes. The neutrophils showed marked toxic granulation. On April 11, 1957, his serum level of SMPZ was 0.8 mg. %. Serum levels had not previously been determined.

After one week of steroid therapy most of the bullae had ruptured, leaving raw denuded areas. Large ecchymotic areas were noted on the patient's arms, legs, and trunk. Over the next seven days intravenously administered hydrocortisone and corticotropin were gradually withdrawn, and the patient was maintained with orally administered prednisolone, 0.5 mg. four times a day, thereafter. This was withdrawn gradually over the next 13 days. The patient was then given corticotropin, 40 units daily, for an additional seven days. On May 3, 1957, one month after the reaction was first noted, the patient received his last steroid therapy.

On May 16, 1957, six weeks after the onset of his reaction, the patient was discharged from the hospital. At that time the skin lesions had all healed. Two weeks later the patient was seen again and appeared completely recovered.

CASE 2.—A 37-year-old white man had previously taken sulfonamide drugs, streptomycin, chloramphenicol (Chloromycetin), chlortetracycline, tetracycline, and penicillin. He gave no history of previous allergic reaction to drug sensitivity. He was given SMPZ, 1.5 gm. initially and then 0.5 gm. once a day. Two days later, after receiving a total dosage of 2.5 gm., he developed scarlatiniform dermatitis. When the drug was discontinued, the dermatitis disappeared in about three days.

CASE 3.—A 58-year-old white man had had penicillin but no other drugs. He had had neither allergic reactions nor any untoward drug reactions. SMPZ was given in an initial dose of 1.5 gm. and a maintenance dose of 0.5 gm. daily. Three days later, after a total dosage of 3.5 gm., the patient developed confluent diffuse blotchy maculopapular erythematous dermatitis over the axillae, back, buttocks, and inguinal areas accompanied by temperature of 102 F. The dermatitis subsided slowly after the drug was stopped.

CASE 4.—A 68-year-old white man had no history of any antibiotic therapy and no previous drug

Patient in Case 1.

sensitivity or allergy. He was given an initial dose of 2 gm. of SMPZ and was then given 1 gm. daily. Four days after the start of therapy, after a total dose of 4 gm., the patient developed diffuse maculopapular erythematous dermatitis over his arms, chest, and groin which subsided about four days after cessation of the therapy.

CASE 5.—A 58-year-old white man had taken sulfonamide medication 15 years previously and had recently taken sulfisoxazole (Gantrisin), without ill effect. Chlortetracycline produced diarrhea; oxytetracycline produced nausea. He gave no history of systemic allergy. His initial dose of 2 gm. of SMPZ was followed by a daily maintenance dose of 1 gm. The patient was also being given isoniazid and aminosalicylic acid. He developed urticaria of the lower extremities after six days of SMPZ therapy which disappeared 24 hours after discontinuance of the drug. The isoniazid and aminosalicylic acid were not discontinued.

CASE 6.—A 73-year-old white man gave no history of any drug therapy except for penicillin, given 10 years previously. He had never had any type of allergy. SMPZ was given in an initial dose of 2 gm. followed by a daily dose of 1 gm. After eight days, and a total dose of 10 gm., the drug was stopped. On the ninth day moderately pruritic morbilliform dermatitis appeared over the entire body. This dermatitis disappeared two days later.

Ambulatory Patients

Of a series of 30 ambulatory patients given SMPZ for chronic urinary infections in doses ranging from 500 mg. once a day to 2 gm. a day, 7 patients (23.3%) developed dermatitis (Table 2). Of these seven patients, three had a history of previous sulfonamide ingestion. One patient gave a history of a reaction to sulfonamide previously, and one patient reported a previous reaction to nitrofurantoin (Furadantin). This patient developed bullous dermatitis due to nitrofurantoin and morbilliform dermatitis due to SMPZ. One patient had morbilliform dermatitis due to nitrofurantoin and no untoward reaction to SMPZ. Of the 22 patients who had no recorded reaction to SMPZ, 15 had previously taken sulfonamides. Case reports of those patients who noted dermatitis follow.

CASE 7.—A 47-year-old white woman had a previous history of allergy to penicillin and sulfonamides. She had been taking sulfamethizole (Thiosulfil) and nitrofurantoin up to five months before the SMPZ was started. She was given 0.5 gm. of SMPZ b. i. d. After five days of such therapy she developed morbilliform dermatitis, which cleared within three days after discontinuance of the drug.

CASE 8.—A 53-year-old white woman was treated with SMPZ, 0.5 gm. b. i. d., for 15 days. She then noticed morbilliform dermatitis. She continued SMPZ therapy for six more days at the same dosage. During this time the dermatitis persisted. SMPZ was then discontinued, and the dermatitis slowly subsided. She had taken sulfisoxazole, phenylazodiamino-pyridine hydrochloride (Pyridium), and sulfamethizole in the past.

CASE 9.—A 40-year-old white woman with no history of previous sulfonamide intake was given 0.5 gm. of SMPZ b. i. d. for 42 days, at which time she noticed vertigo and papuloerythematous dermatitis on her forehead. This subsided promptly on discontinuance of the drug.

CASE 10.—A 59-year-old white woman had previous vesicular dermatitis due to nitrofurantoin. She had taken tetracycline, with no untoward reaction. She was given SMPZ orally, 1 gm. a day, and after 14 days of such therapy she developed pruritic petechial dermatitis, more pronounced in the areas exposed to the sun. This eruption subsided slowly on discontinuance of the SMPZ.

CASE 11.—A 48-year-old white woman was given 0.5 gm. of SMPZ three times a day for 14 days, and she developed morbilliform papular erythematous dermatitis, which disappeared three days after discontinuance of the drug.

CASE 12.—A 63-year-old white woman was given 0.5 gm. of SMPZ three times a day. On the 14th day of therapy, petechial dermatitis was noted, which subsided after the drug was discontinued.

TABLE 2.—*Reactors in Ambulatory Series*

Case No.	Previous Sulfonamides	Daily SMPZ Dose, Gm.	Total Dose, Gm.	Time of Onset, Day	Symptoms	Time to Clear After Drug Stopped
7	Yes (reacted)	1	5	5	Dermatitis	3 days
8	Yes	1	21	15	Dermatitis	About 10 days
9	No	1	42	42	Dermatitis	Not recorded
10	No (previously reacted to nitrofurantoin)	1	14	14	Dermatitis	Not recorded
11	No	1.5	21	14	Dermatitis	Not recorded
12	No	1.5	21	14	Dermatitis	Not recorded
13	Yes	1.5	7.5	5	Dermatitis	See text

CASE 13.—A 19-year-old white woman, who in the past had had sulfamethizole and chloramphenicol therapy, was given SMPZ, 0.5 gm. twice a day. Five days later she developed papuloerythematous dermatitis with burning and itching. She discontinued the SMPZ, and the dermatitis cleared. Two days thereafter she reinstituted SMPZ therapy at the same dosage, and the dermatitis and burning promptly returned, only to clear again when the drug was stopped. The patient was again given SMPZ, a dose of 250 mg. once a day, with no return of the dermatitis.

Comment

Previous administration of sulfonamides does not appear to influence the incidence of untoward reactions but would appear to determine the time of onset of the reactions when they occur. Five of the thirteen patients with untoward reactions to SMPZ developed them after about two weeks of 1 gm. or more, daily ingestion. Four of these five patients gave no history of previous intake of sulfonamide drugs. Six of the thirteen patients with untoward reactions developed them in less than seven days. Four of them had previously taken sulfonamides. The other two patients developed dermatitis after 1 gm. daily doses for 9 days and 42 days, respectively. They had not previously taken sulfonamides.

Only 2 of 30 patients taking 0.5 gm. daily had reactions. These were part of the hospitalized group. Reactions occurred after two and four days, respectively. These findings would suggest a possible relation to the dosage which subsequent studies have seemed to further substantiate.

Daily serum SMPZ determinations did not show a gradual increase with time at a constant dosage but averaged around 10 mg. % in those patients taking 1 gm. daily doses and 5 mg. % in those patients receiving 0.5 gm. daily. There were wide variations from these mean values, however. No correlation between reactions and serum SMPZ levels was possible, because an insufficient number of determinations was made.

It is possible that the outpatient series had a higher percentage of reactions because outpatients were all taking a greater daily dose. In the total series of 85 patients, 2, or 0.66%, of 30 patients taking 0.5 gm. daily doses showed an untoward reaction, while 11, or 20%, of 55 patients taking 1 gm. or more daily developed untoward reactions.

The patient in Case 13 developed dermatitis that apparently had a definite relationship to the dose. She had taken sulfonamide drugs before, although she had reported no reaction.

These untoward reactions to SMPZ are similar to reported reactions to other sulfonamides in many respects. Pomeranz and Kirschner [7] state that, for the most part, reactions of sulfonamide hypersensitivity are highly specific for the particular substance used, but 15% of patients sensitized to one sulfonamide will react to any other sulfonamide. Schlesinger et al.[8] reported on the natural history of sulfonamide morbilliform dermatitis in children. He found that the eruption began within 5 to 17 days, with a 3- to 72-hour prodromal period of fever, and that the dermatitis lasted from 36 to 96 hours but tended to last longer in those cases where the drug was not discontinued at once. Hageman and Blake [9] found that dermatitis occurred commonly between the seventh and ninth day after the sulfonamide therapy was started. Fever was associated with the eruption in about half of the cases. Of the 3470 patients with reactions to sulfonamides reported by Dowling and Leper,[10] similar time relationships were noted. These authors also felt that, when untoward reactions occurred, the prompt stopping of sulfonamide therapy was important in preventing serious reactions.

In the patients of Volini et al.,[11] there was no definite correlation between the blood sulfonamide level and the development of dermatitis. However, the average total dose given reactors was higher than the average for the nonreactors. Keefer [12] felt that dermatitis appeared at one of three periods following the administration of

sulfonamides. 1. The usual time was between 7 and 9 days after the drug was started, although the lesions might appear as early as the 4th or as late as the 14th day. 2. Dermatitis would occur as a prompt or accelerated reaction within 24 hours after the drug was started. 3. The dermatitis might occur late, that is, two to six weeks after the institution of therapy. When the skin eruptions were prompt they would almost invariably occur in persons who had previously received the same or a closely related drug.

Conclusions

The extent to which the severity and incidence of these untoward reactions are related to dosage was thought important enough to merit discussion. The data herein presented seem to indicate a relationship to dosage in some cases but not in all. If daily doses of 0.5 gm., or less, are given, a lower incidence of reactions may be expected.

In general, if a reaction is going to occur, it will occur within 1 to 5 days if the patient has taken sulfonamides previously, whereas in those who have not had previous sulfonamide medication around 14 days is a common time of onset.

Except for the one instance of severe dermatitis the reactions were mild, consisting of fever and/or dermatitis, and they usually disappeared within three or four days.

Summary

Of 55 hospital inpatients and 30 outpatients receiving orally administered sulfamethoxypyridazine therapy for urinary tract infections, 10.9% of the former and 12.7% of the latter developed untoward reactions, mostly dermatitis. One case of a very severe reaction was recorded. If the 85 patients are grouped according to daily dosage received, 0.66% of 30 patients taking 0.5 gm. in daily doses showed untoward reactions, while 23.7% of 55 patients taking 1 gm. or more in daily doses developed untoward reactions. Othewise no statistically significant correlations were found among the variable features of the untoward reactions in this series of 85 patients.

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The Irritating and Sensitizing Capacity of Epoxy Resins

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During the past few years there has been a rapid development in the chemical technology of epoxy resins. Currently, these resins are being widely manufactured and are available under a variety of trade names.

Industrially the epoxy resins are important for use in corrosion-resistant surface coatings, molding compounds, castings, laminating or reinforcing plastics, encapsulating electronic circuits, and adhesives, as in metal-to-metal bonding.

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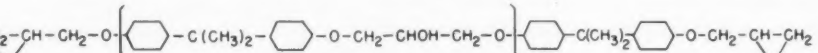
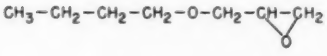
The generic name of these compounds is derived from the fact that they are polyethers with terminal epoxy groups. In general, they are condensation products of epichlorohydrin with *p,p'*-isopropylidenediphenol (bisphenol A) and have the type of chemical structure shown in the Figure (*a*). They have a wide range of viscosities, i. e., they range from low-viscosity liquids to high-melting-point solids. Commercial epoxy resins of the low-viscosity type usually contain, in addition to the high-molecular-weight resin, an epoxy resin modifier of low molecular weight, such as that shown in the Figure (*b*). The desirable properties of these resins are obtained only after they are combined with curing agents

a.



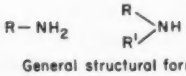
General structural formula for EPOXY-RESINS of high molecular weight

b.



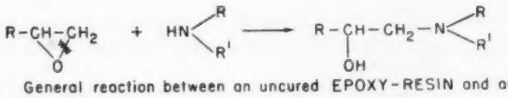
Structural formula for EPOXY-RESIN modifiers of low molecular weight derived from butanol

c.



General structural formula for primary and secondary amine curing agents (hardeners)

d.



General reaction between an uncured EPOXY-RESIN and an amine curing agent (hardener)

General structural formulas and chemical reaction of materials used in epoxy resin formulations.

and thus converted into mechanically strong polymers.

The curing agents (hardeners) for the self-hardening epoxy resin formulations are polyfunctional amines containing primary and secondary amino groups, as indicated in the Figure (*c*). These agents also range in viscosity from liquid to solid.

Prior to combination with the curing agents the resin is referred to as an uncured resin, whereas after this combination it is a cured resin. The curing process (the Figure, *d*) is a result of the reaction of the amine hardener with the epoxy resin to form a high-molecular-weight cured resin. The epoxy resin modifier undergoes this same type of curing reaction with the amine curing agent. The curing reaction is carried out at room temperature and is complete in one to five hours.

The increasing use of these resins in various industrial processes has resulted in a high incidence of contact dermatitis. The clinical aspects of dermatitis resulting from the use of epoxy resins have been reported by several workers.[1-7] Grandjean[8] reported the occurrence of dermatoses in 43% of all workmen in 11 factories where the epoxy resins were in use. Malten[9] reported a sensitization rate of 10% in workers processing the epoxy resins.

Because of the paucity of information concerning the toxicology, skin irritancy, and sensitizing capacity of the materials used in the formulation of epoxy resins, an investigation of these problems was initiated in this laboratory. The results of animal toxicity will be the subject of another report.[10] The present report deals with the results secured by patch testing human volunteers to an uncured epoxy resin, an uncured epoxy resin modifier, and four amine curing agents.

Materials

The materials* used in this investigation can be divided into three categories: (1) uncured epoxy resin (CD 15003); (2) uncured epoxy resin modifier (CD 15004 B), and (3) amine curing agents (CD 16005, CD 16009, CD 16019 A, XH 173-50).

Uncured Epoxy Resin.—CD 15003† is a low-viscosity modification of an epoxy resin obtained by the condensation of epichlorohydrin with *p,p'*-isopropylidenediphenol and has the general structure illustrated in the Figure (*a*). It is a pale-amber liquid resin containing 2,3-epoxypropyl ethers of both diphenols and aliphatic alcohols. No free phenolic groups are present. It is soluble in aromatic hydrocarbons and ketones and insoluble in water. This material is representative of similar modified commercially available epoxy resins used in industrial applications.

Uncured Resin Modifier.—CD 15004 B is a commercially pure grade of 2,3-epoxypropyl ether of *n*-butyl alcohol. It is a light-colored thin liquid soluble in alcohol and acetone but only slightly soluble in water.

Amine Curing Agents (Hardeners).—CD 16009‡ is an adduct of a polyaliphatic amine containing primary and secondary amino groups and aliphatic hydroxyl groups. It contains no metallic salts. The material is insoluble in aromatic hydrocarbons, soluble in alcohol, and slightly soluble in cold water.

CD 16005 is an adduct of ethylene oxide with diethylenetriamine and contains primary and secondary amino and hydroxyl groups. It is insoluble in aromatic hydrocarbons, soluble in alcohol, and soluble in cold water.

CD 16019 A is an adduct of a polyaliphatic amine which contains primary and secondary amino groups and aliphatic hydroxyl groups. It contains no halogens and no metallic salts. This material is insoluble in aromatic hydrocarbons, soluble in alcohol, and slightly soluble in cold water.

XH 173-50 is an experimental hardener which contains primary and secondary aliphatic amino groups and aliphatic hydroxyl groups. It contains no halogens, no benzene-ring structure, and no metallic salts. This material is insoluble in aromatic hydrocarbons, soluble in alcohol, and slightly soluble in water.

Methods

The technique employed for patch testing was that suggested by Schwartz.[11] The material to be tested was suspended in liquid petrolatum and adsorbed to a ½ in. square cotton patch. This was placed in contact with the skin and covered with a cellophane insulation ¾ in. square. An occlusive

* All materials used in this investigation were furnished by Ren Plastics, Inc.

† Resin in laminating mix RP-1130, Technical Bulletin 1001 R, Ren Plastics, Inc.

‡ Curing agent (hardener) in the "1700" series of epoxy resins, Technical Bulletin 1001 R, Ren Plastics, Inc.

TABLE 1.—*Irritancy Reactions Obtained by Patch Testing Twenty-Five Human Subjects to Two Resinous Materials*

Concentration, %	Uncured Resin (CD 15003)		Resin Modifier (CD 15004 B)	
	PR/NT *	%	PR/NT *	%
100	12/25	48	5/5	100
10	2/25	8	17/25	68
5	0/25	0	8/25	32
2.5	0/25	0	1/25	4
1.25	--	--	0/25	0

* Positive reaction per number of subjects tested.

patch of adhesive tape measuring 1×3 in. was used to cover the cellophane. The patches as described were applied to the subjects' backs. Several concentrations of each compound were used. Unless the subject complained of irritation the patch was left in place for 48 hours, with the subject refraining from bathing during this period. The patch was then removed, and the reaction, recorded. Reactions were classified according to the following gradations:

Negative	No reaction
+	Erythema
++	Erythema and induration
+++	Erythema, edema, papules, and/or vesicles
++++	Erythema, edema, multiple vesiculation, and/or superficial ulceration

Fourteen days after the irritancy tests had been completed sensitization tests were done. Each subject was tested with a concentration of each compound previously proven to be nonirritating. These tests were read 24 and 48 hours after application of the material and again after 5 days.

Test subjects, both men and women, were members of the white race and ranged in age from 23 years to 34 years. Each compound was tested on 25 subjects.

Results

The data obtained in this investigation are divided into two parts: (1) irritancy studies and (2) sensitization studies.

Irritancy Tests.—Uncured Epoxy Resin (CD 15003, Table 1): Twelve subjects (48%) reacted to this compound. Reactions ranged from + to +++. Two subjects (8%) reacted to concentrations less than 100%. There were no reactions to concentrations of less than 10%.

Uncured Epoxy Resin Modifier (CD 15004 B, Table 1): A pilot study on five subjects indicated that in a concentration of 100% this compound produced a ++++ reaction in all subjects tested. Therefore, concentrations of 10%, 5%, 2.5%, and 1.25% were used for further tests. In a concentration of 10% 17 subjects (68%) reacted to this compound. Eight subjects (32%) reacted to a concentration of 5%, and one subject (4%) reacted to a concentration of 2.5%. Reactions ranged from + to ++++.

Amine Curing Agents (Table 2): Compound CD 16005. Eleven subjects (44%) reacted to a concentration of 100%. One subject (4%) reacted to a concentration of 10%. There were no reactions to concentrations less than 10%. Reactions ranged from + to +++.

Compound CD 16009. Ten subjects (40%) reacted to a concentration of 100%. Only one subject (4%) reacted to a concentration of 10%, and there were no reactions below this concentration. Reactions ranged from + to +++.

Compound 16019 A. A pilot study of five subjects indicated that at a concentration of 100% this compound produced a ++++ reaction in all subjects. Sixteen subjects (64%) reacted to a concentration of 10%. Nine subjects (36%) reacted to a concentration of 5%, and three subjects

TABLE 2.—*Irritancy Reactions Obtained by Patch Testing Twenty-Five Human Subjects to Four Amine Curing Agents*

Concentration, %	CD 16005		CD 16009		CD 16019 A		XH 173-50	
	PR/NT *	%	PR/NT *	%	PR/NT *	%	PR/NT *	%
100	11/25	44	10/25	40	5/5	100	4/25	16
10	1/25	4	1/25	4	16/25	64	0/25	0
5	0/25	0	0/25	0	9/25	36	0/25	0
2.5	0/25	0	0/25	0	3/25	12	0/25	0
1.25	--	--	--	--	0/25	0	--	--

* Positive reaction per number of subjects tested.

TABLE 3.—*Sensitization Reactions Obtained by Patch Testing Twenty-Five Human Subjects to the Component Materials Used in Epoxy Resin Formulations*

Component	Material	Reactions PR/NT *	%
Uncured resin	CD 15003	5/25	20
Resin modifier	CD 15004 B	5/25	20
Curing agent	CD 16005 B	3/25	12
Curing agent	CD 16009	3/25	12
Curing agent	CD 16019 A	3/25	12
Curing agent	XH 173-50	0/25	0

* Positive reaction per number of subjects tested.

(12%) reacted to a concentration of 2.5%. There were no reactions at a concentration of 1.25%. Reactions ranged from + to ++++.

Compound XH 173-50. Four subjects (16%) reacted to a concentration of 100%. No subject reacted to less than a 100% concentration. Reactions ranged from + to ++.

Sensitization Tests (Table 3).—Uncured Epoxy Resin (CD 15003): Five subjects (20%) had positive reactions to this compound.

Uncured Epoxy Resin Modifier (CD 15004 B): Five subjects (20%) reacted to this compound.

Amine Curing Agents: Compounds CD 16005, CD 16009, and 16019 A. Each of these compounds produced a positive reaction in three subjects (12%).

Compound XH 173-50. This compound did not produce a single sensitization reaction.

Comment

Previous reports regarding epoxy resins have dealt with a consideration of the types of cutaneous manifestations they produce and the incidence of dermatitis occurring in the exposed personnel without regard to a consideration of the individual components of the resin formulations.[2,8] The present investigation has attempted to assess in a general manner the irritating and sensitizing capacity of the component materials in the epoxy resin formulations.

Table 4 correlates the number of positive irritancy and sensitization tests for each of the compounds studied. The irritating capacity of the uncured epoxy resin modifier, CD 15004 B, (68%) was greater than that of the uncured resin, CD 15003 (48%). Both compounds produced positive sensitization tests in 20% of the subjects. Hine et al.[12] recently reported no irritation or sensitization reactions in humans who were patch-tested to cured epoxy resins. It should be pointed out that the reason different results were obtained in this investigation is that the resinous materials (CD 15004 B and CD 15003) studied were in a different chemical state, i. e., uncured epoxy resins.

Compound CD 16019 A was the most irritating (64%) of the amine curing agents. Compounds CD 16005 (44%) and CD 16009 (40%) were comparable in their irritating capacity. Each of these three compounds, although differing in irritating capacity, produced a positive sensitization reaction in 12% of the subjects tested. Compound XH 173-50, an experimental curing agent, produced positive irritancy tests in only 16% of the subjects. There were no sensitization reactions to this compound.

It is interesting to note that of the four amine curing agents tested, the experimental compound (XH 173-50) was the least irritating and sensitizing. This would seem to indicate that amine curing agents may be developed which are less irritating and sensitizing than those currently being used.

Summary

The irritating and sensitizing properties of one uncured resin, one uncured resin

TABLE 4.—*Comparative Data on the Irritating and Sensitizing Capacity of the Six Materials Studied*

Component	Material	Irritancy Tests Positive Reactions	%	Sensitization Tests Positive Reactions	%
Uncured resin	CD 15003	12	48	5	20
Resin modifier	CD 15004 B	17	68	5	20
Curing agent	CD 16005 B	11	44	3	12
Curing agent	CD 16009	10	40	3	12
Curing agent	CD 16019 A	16	64	3	12
Curing agent	XH 173-50	4	16	0	0

modifier, and four amine curing agents were studied by means of human patch testing.

The uncured resin and the resin modifier were found to be irritating and sensitizing with use of the closed patch technique and 48-hour contact.

Three of the four curing agents tested were irritating but less severe sensitizers than the resins.

The amine curing agent (XH 173-50) was found to have low irritancy and failed to produce any sensitizing reaction.

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Mucinous Metaplasia in Normal Apocrine Glands

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The apocrine glands are specialized structures which normally produce a whitish fluid containing carbohydrate and protein. This fluid is said to be produced by the ejection of part of the cellular protoplasm of the secretory cells into the lumen of the glands. The material in the fluid forms a solid white mass when it dries at the surface. It has been assumed usually that this is a constant product, as no variations in its content or manner of production have been documented. The attempts to correlate function of the apocrine glands with various cycles of the body have been summarized by Montagna.[1] He showed that no specific correlation existed between the menstrual cycle and the activity of the glands.

One of us (R. K. W.) and associates[2,3] have described a Schiff-reactive, diastase-resistant, mucin-positive, nonmetachromatic material in the apocrine glands in Fox-Fordyce disease. In such cases the mucin was not confined to the glands but was free in the stroma of the tissues and appeared to be related to the inflammatory infiltrate. Montagna has shown that cystic dilatation occurs more and more frequently as the apocrine glands age. Such a change is not a requisite one with senescence and may not be present even in extreme old age, but it appeared to Montagna that the number of cystic glands increased as the age of the subject increased. He noted a diastase-resistant, Schiff-reactive, metachromatic material within the cystic glands. While investigating other axillary lesions, such as acanthosis nigricans, we observed similar cystic mucinous changes and decided to tabulate the incidence of mucinous change in apocrine glands in the human axillae. A similar study of variations from normal structure of the eccrine glands was made by Holyoke and Lobitz.[4]

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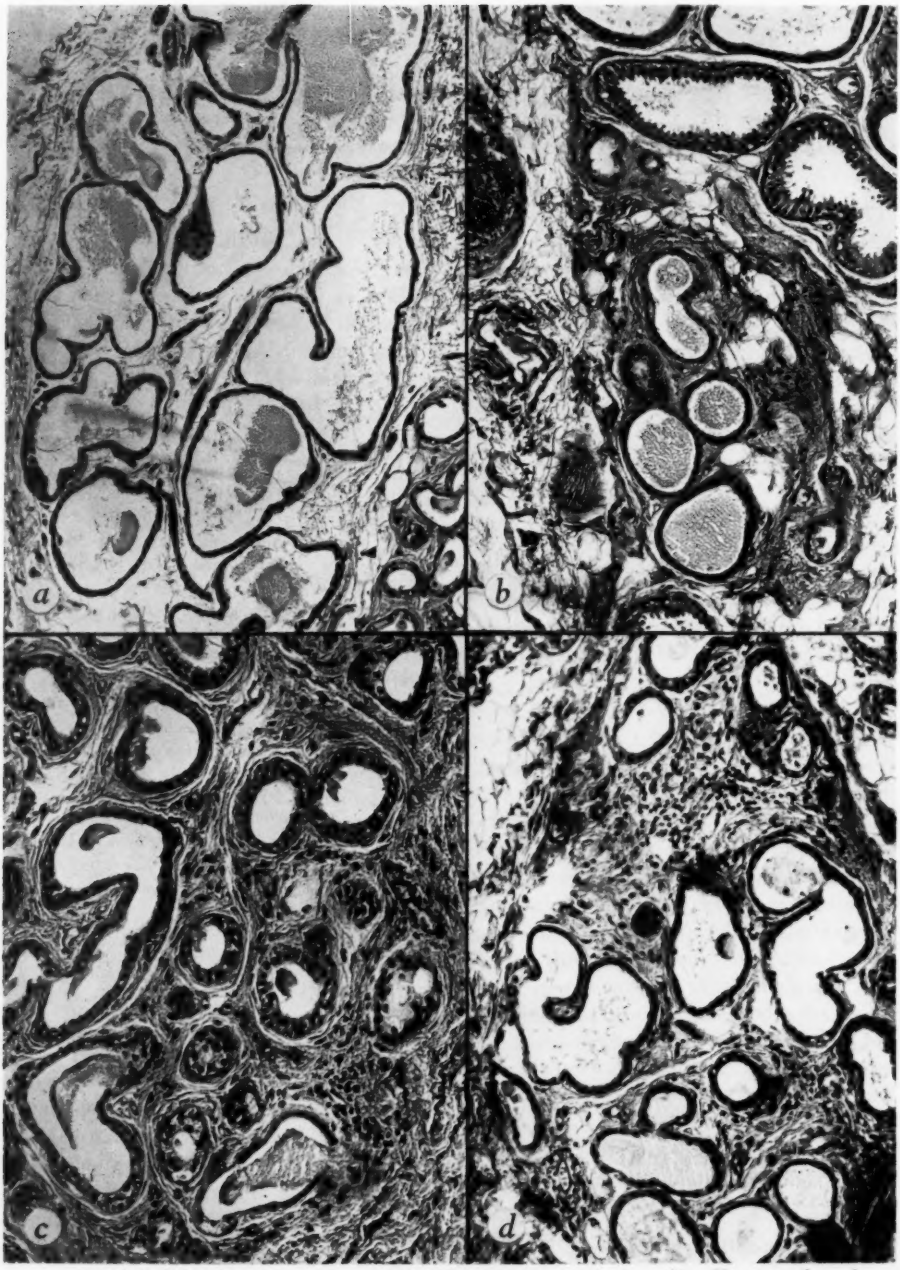
Methods and Material

Specimens 2 cm. in length were obtained deep to the panniculus in the axilla at consecutive necropsies when there were no pathologic findings in the axilla. These specimens were fixed immediately in 10% formalin and embedded in paraffin. The first sections were cut and stained with hematoxylin and eosin. When indicated by observation of sections stained with hematoxylin and eosin, additional sections were cut and stained with toluidine blue, Mayer's mucicarmine, or the periodic acid-Schiff (PAS) method with and without diastase. Best's carmine stain was used in 10 instances, as was Sudan black B. From specimens in which the first sections stained with hematoxylin and eosin did not show pathologic change or deviation from normal structures, additional sections were prepared on two separate occasions, so that in all more than half of each block was sampled when necessary. Specimens from a total of 100 cases were studied, and the incidence of cystic dilatation, the presence of mucin, and other pathologic changes were recorded.

Results

Cystic dilatation with mucinous metaplasia of the apocrine gland was observed in the first sections cut from the specimens and stained with hematoxylin and eosin in 43 of the 100 cases. In 18 additional cases cystic dilatation and mucinous change were observed on cutting deeper into the blocks of tissue. In each instance the positive results were confirmed by staining with the specialized methods mentioned. Observations showed uniformly a mucin-positive, Best's carmine-pink, PAS-positive, dia-



(*a* and *b*) Dilated cystic apocrine glands with mucinous casts in the axilla. Hematoxylin and eosin; × 95. (*a*) From a man 80 years old. Mucinous central casts may be noted. (*b*) From a boy 10 years old. The mucinous casts are adjacent to normal glands. (*c*) Progressive atrophy of apocrine epithelium with mucinous cast formation. Some vacuolar degeneration is visible in almost every coil. Hematoxylin and eosin; × 170. (*d*) Early granuloma formation about a cystic apocrine gland. Hematoxylin and eosin; × 140.

Mucinous Change in Apocrine Glands Related to Age

Age, Yr.	Total Cases	Mucin-Positive			Mucin-Negative		
		Male	Female	Total	Male	Female	Total
0–10	7	1	0	1	5	1	6
11–20	2	1	1	2	0	0	0
21–30	4	1	1	2	2	0	2
31–40	7	1	4	5	2	0	2
41–50	11	6	3	9	2	0	2
51–60	19	6	5	11	6	2	8
61–70	20	12	4	16	2	2	4
71–80	17	5	4	9	5	3	8
81–90	12	3	3	6	2	4	6
91–100	1	0	0	0	0	1	1
Total	100	36	25	61	26	13	39

stase-resistant, orthochromatic-toluidine blue material. Fat was not found in the cystic material in any significant quantity. These changes are illustrated in the Figure, in (*a*).

The total number of observations is recorded by decades in the Table. Although it is readily apparent that the number of samples as they pertain to the several decades of life is not statistically significant, certain facts are apparent. The mucinous cystic dilatation of the apocrine glands may be observed early in life. The youngest age at which mucinous cystic dilatation was observed in our series was in the case of a boy aged 10 years (the Figure, [*b*]). In specimens obtained from persons in the third through the ninth decades the number of positive results increased (Table). The total number of positive results was 61 out of the 100 sampled in all age ranges.

Specimens from a total of 38 females were available for study. Of these, 25 showed mucinous change. Interestingly enough, all sections examined from the oldest woman in the study were normal. Of the tissue studied from 62 males, that from 36 showed mucinous change. The small number of figures for males and females in each decade permits no specific interpretations; yet for the most part one-half to two-thirds of each group had mucinous apocrine glands.

The apocrine glands studied from the very young were completely normal, though rudimentary. The specimens came from a female fetus in the seventh month of gestation and from five boys, one 12 hours old, two 1 month old, one 3½ months old, and one 11 months old. We agree with Montagna's statement that definite but rudimentary apocrine glands exist in early life and are not only a pubertal development.

Other changes including atrophic epithelium were present in the glands showing the cystic mucinous change. This change apparently was present in secretory coils adjacent to coils which still had a normal but vacuolated appearance, as in the Figure, (*c*). Inflammation was present about the glands in six instances. In two of these, inflammation had proceeded to granuloma formation with histiocytic cellular change, as in the Figure, (*d*). On one occasion, acute inflammation was noted within the gland. In one instance cystic mucinous material was found in a duct. The presence of superficial mycosis was noted on the verrucous surface of one axillary specimen. In four specimens cyst formation of the apocrine glands without mucinous metaplasia was noted. In each of these the apocrine gland itself was atrophied and a thin eosinophilic material filled the lumen of the atrophied gland. This material was not mucin- or PAS-positive. In one instance the wall of the gland had ruptured and a small granuloma surrounded the rupture. No mucinous changes were found in the stroma surrounding the glands. Metachromatic material was observed routinely in the papillary dermis of the specimens. It was distinct from the material found in the cystic glands.

Comment

The existence of a mucinous cystic change in the apocrine glands of normal

skin indicates that the observation of such changes in pathologic conditions needs to be reevaluated. This same change was found in five cases of Fox-Fordyce disease. Its relation to this disease was considered to be of some significance. In this disease process the mucinous material was found free in the dermis, and it was postulated that this might form the basis of the lesion observed. Certainly the glandular mucinous change by itself is normal, as shown by this study. Eccrine and apocrine glandular tumors may form mucinous material within their lumina, as shown by Lennox and co-workers.[5] Primitive mucinous metaplasia has been reported in a sweat-gland tumor by Walther and Montgomery.[6] Such a mucinous change has been thought to be some atavistic property of glandular epithelium, as most glands in lower animals produce mucus. Recently Hambrick[7] reported PAS-positive material in eccrine glands.

The fact that 61 of 100 specimens of apocrine glands showed these mucinous changes is important. It raises the question whether the apocrine glands normally go through a mucinous stage in some phase of their development or function. If a mucinous apocrine gland exists in most normal persons, this must be considered a normal phase of the life history of the apocrine gland. Whether this is a degenerative phenomenon or the result of the exhaustive overactivity cannot be stated. The fact that mucinous cystic changes are found in the same secretory coil with vacuolated glandular epithelium suggests that these changes are indicative of a progressive stage of degeneration of the gland and, therefore, that some form of cycle exists in the apocrine gland. This would not be a hormonal cycle, as has been postulated on many occasions, but rather an anatomic cycle related to function.

The youngest person in our series in whom these mucinous cystic changes were found was a 10-year-old boy. This indicates that this mucinous change is present early in life and is not necessarily a change of senescence or aging. Perhaps, too, this supports the idea that the mucinous change is a part of a definite cyclic anatomic structural alteration of the apocrine gland. There is no question, as Montagna has stated, but that the incidence of mucinous changes increases with age. Mucinous changes, however, do not necessarily occur with age, as the oldest patient in our series had small but normal apocrine glands. The incidence of this change decreased in the last two decades in our group. Therefore, this is an alteration which need not be present but, from the age of 20 years on, may be found in axillae of many persons. What physiologic factors affect it can only be surmised at present. It would be interesting to examine specimens after prolonged adrenergic stimulation of the normal axilla to see whether this change had been induced.

Mucinous changes in the apocrine glands of the normal axilla should be interpreted with caution in terms of pathology. What their physiologic or pathologic significance may be is not clear. When mucin is free in the dermis, it has pathologic significance, but when it is confined to glandular atrophic structures its significance cannot be readily appreciated in terms of cutaneous disease. Most probably mucinous changes in the gland do not represent a diseased state but a normal physiologic alteration in the glandular structure.

The range of changes in the normal gland corresponds closely with that described by Holyoke and Lobitz[4] for the eccrine gland. They found (1) cystic atrophic changes without mucinous change, (2) granuloma formation, and (3) nonspecific inflammatory infiltrate related to some of the apocrine glands. One instance of pyogenic infection was found in an otherwise normal apocrine gland. No mucin was found in relation to this gland or its neighbors. Thus, the mucinous change does not appear to be related to inflammation.

Summary

Mucinous metaplasia occurs in grossly normal axillary apocrine glands as determined from specimens obtained at necropsy. The mucin is Schiff-reactive, diastase-resistant, and toluidine blue orthochromatic. It was found in 61 of 100 samples of normal axillary skin from persons of all decades of life. It was found as early as age 10 years and was more frequent with increasing age. It seems possible that this might be a normal physiologic change of the axillary apocrine glands. The pathologic significance is discussed.

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Reflex Sympathetic Dystrophy

Report of a Case

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The production of a disordered sympathetic response, alteration in circulatory dynamics, and restriction of function from minor trauma is not a common occurrence. The presentation of the following case emphasizes the necessity for dermatologists to be aware of such a syndrome.

Report of Case

A 24-year-old white longshoreman was seen on July 6, 1957, because of persistent swelling of his left hand of five months' duration.

He stated that on Feb. 24, 1957, while loading a ship, he cut the middle finger of his left hand on a drum of oil. He was seen by a physician, who applied a Band-Aid and gave him daily injections of penicillin intramuscularly for one week. An x-ray of the finger was reported as "negative." About one week after the accident, he started to have a throbbing pain in his hand. A few days later his hand became swollen and red. In spite of antibiotics, splinting of the affected extremity, and hydrotherapy he had no improvement. He stated that at no time had his temperature been elevated.

During this period, he has noticed a gradual restriction in his ability to completely flex his fingers. In spite of the discomfort he has continued working at his job. He added that he discovered the throbbing in his hand diminished if he carried his arm in a sling.

Past History.—There is no history of hay fever, asthma, or eczema. The patient has had no operations, accidents, or illnesses; he denies the use of drugs. He has no food allergies.

Physical Examination.—The patient was 6 ft. 1 in. tall and weighed 210 lb.; temperature was 98.6 F; pulse rate was 70, and pulse was regular and of good quality. The blood pressure was 110 systolic, 68 diastolic. Positive findings on the physical examination were as follows.

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The skin of the left hand and fingers was erythematous and definitely warmer than that of the right hand. There was soft pitting edema on the dorsum extending to the wrist; it involved all the fingers except the thumb. There were no motor or sensory changes; flexion of the fingers was limited to about 30 degrees. There was a linear healed one-half in. scar at the base of the left middle finger on the dorsal aspect. The scar was soft and pliable. No induration was present. There was no epitrochlear or axillary adenopathy.

Laboratory Results.—Examination of the blood showed a white blood cell count of 6200, with 80% neutrophils; hemoglobin was 13.2 gm. per 100 ml. The hematocrit was 41%; the erythrocyte sedimentation rate was 16 mm. in one hour (Westergren). The urine was normal. An x-ray of the left hand was negative. The nonprotein nitrogen was 25%; the total protein, 7 gm.; the albumin, 4.2 gm., and the globulin, 2.8 gm. A blood Hinton test was negative.

Diagnosis and Treatment.—A diagnosis of reflex sympathetic dystrophy following minor trauma was made. Oral ganglionic blocking agents were given in increasing dosages to the point of tolerance for several weeks, without clinical or symptomatic relief.

In view of the favorable reports of Betcher et al.[1] on the treatment of this syndrome by continuous procaine block of the paravertebral sympathetic ganglions, the patient was transferred for such therapy.

After three days of treatment the patient was free of his pain; the erythema and edema disappeared, and the patient had complete restoration of function. He has remained well to date.

Comment

The functional relationship between the sympathetic nervous system and many disease syndromes is well established. The exact nature of this relationship is not so well known[2]; clinically, however, interruption or cessation of this activity results in remission, amelioration, or cure of the disease syndrome.

Reflex sympathetic dystrophy may be defined as an excessive or abnormal response of an extremity to injury and is manifested by four constant characteristics: excessive and unduly prolonged pain, vasomotor disturbances, delayed functional recovery, and trophic changes. Included in this pattern of response are such terms as causalgia, Sudeck's atrophy, post-traumatic pain syndrome, and traumatic edema. According to Casten,[3] all of these different entities have the same basic etiology; they vary only in degrees of severity. Reflex sympathetic dystrophy, therefore, is an all-inclusive term for the above syndromes and connotes the basic etiology involved in all of these entities.

Originally described by Percival Potts[4] in the late 18th century, this pattern of response was emphasized by Denmark[5] in 1813. Weir Mitchell[6] in 1864 and Sir James Paget[7] gave classical descriptions of the severest form. The former coined the descriptive term causalgia, literally, a burning pain. Later, in 1900, Sudeck[8] described a form characterized by atrophy and osteoporosis.

Etiologically, the response may be elicited by a very trivial and often overlooked injury to the skin or soft tissue or it may be one of great magnitude. It would appear that regardless of the severity of the injury it must of necessity stimulate and injure the nerve fibers particularly of the sympathetic system. Of great interest is why identical trauma may in one person initiate an orderly response while in another the response is disorderly and chaotic. One can only assume that trauma to an extremity sets up afferent sympathetic as well as somatic impulses of different intensities. On the basis of the experimental work of Bingham,[9] one can assume that there are variations in number, distribution, and type of the sympathetic nerve fibers in the extremities.

With afferent impulses of greater intensity entering the spinal cord, a spread of excitation occurs, and synapses are formed between sympathetic and somatic afferent fibers and central efferent fibers of all types. This, no doubt, may be the reason for the pain and vasomotor disturbances in reflex sympathetic dystrophy. The multiple factors that are perpetuated in this syndrome are at least three in number: (1) the variations in individual cerebral integration and response to pain, (2) the relationship between the hypothalamus and the cerebral sympathetic centers, and (3) the activity of the internuncial pool.

It would appear that preformed cerebral patterns of response vary from person to person. Identical stimuli will usually produce responses that resemble these preformed patterns and are only slightly related to the severity of the stimulus. Hypothalamic reactivity also varies, as White[10] has pointed out, and it may be that this accounts for variations in the perpetuation of the response.

In addition, alterations in the so-called internuncial pool, according to Livingston,[11] are significant in accounting for differences in the extent of the spread of excitation and in the number and types of reflex mechanisms which perpetuate the syndrome and thus set up a vicious cycle.

The sympathetic system is an integral part of the homeostatic mechanism of the human organism. It acts through a variety of mechanisms but essentially by regulating body heat; it is responsible for variations in the capacity of the peripheral vascular bed. Thus, in the healthy subject this vasomotor regulatory function of the sympathetic nervous system constitutes its principal function.

Vasomotor activity is constant. Both vasoconstriction and vasodilatation are sympathetic functions. Thus, under conditions of normal physiological demands or altered demands resulting from local trauma or infection, the sympathetic system provides proper temperature control and permits variations in blood flow to satisfy local demands.

Hyperactivity of the system due to local stimuli is seen in the various acute obliterative diseases of arteries and veins and in the chronic obliterative arterial diseases. Local pathological disturbances (anoxia, infection, trauma) set up a constant bombardment of sympathetic centers and result in a massive outflow of vasoconstrictor impulses. This, in turn, results in increased activity of other reflex mechanisms. Once initiated, this state of hyperactivity is perpetuated by defects in central integration of response.

If the above concepts are understood, one can approach treatment on a more rational and a physiologic basis. The beneficial effects of sympathetic interruption in peripheral vascular disease, hypertension, post-traumatic syndrome, etc. are both clinically and experimentally well established.

There are three principal methods of achieving this result: (1) surgical ganglionectomy, (2) chemical block of the paravertebral ganglions by direct infiltration, and (3) pharmacologic interruption with adrenolytic or ganglionic blocking agents.

The following classification adopted by Betcher et al. serves as an excellent base line for determining therapy. It should be emphasized that the following criteria are present in all cases—they differ only in severity: pain, vasomotor disturbances, delayed return of function, and trophic changes.

In Grade I, clinically, pain is the presenting symptom. The onset is usually a few hours after injury, occasionally days, and rarely weeks. It is of maximal intensity, severe, unrelenting, aggravated by emotional or physical disturbances, and not relieved by rest. Vasomotor changes are also severe and may result from vasoconstriction or vasodilatation. Voluntary fixed immobility of the extremity results and, if long continued, trophic changes of skin, subcutaneous tissue, muscle, and bone appear. Early surgical sympathetic interruption is necessary in patients in this group.

Grade II represents a milder form, slower in evolution and, as a result, of longer duration. The pain is dull, throbbing, and aggravated by motion. To ease the pain, the patient voluntarily immobilizes the extremity. In time atrophy develops, and bone involvement is not uncommon. Along with the atrophy and osteoporosis, functional dystrophy appears and may become permanent.

In this type, early institution of continuous procaine paravertebral ganglion blocks may arrest the disease before functional impairment becomes severe or permanent. If no improvement occurs, such cases should have surgery. In the cases of Betcher et al. blocks were continued 14 to 21 days in 54 patients. Of this number, 11 failed to improve and were subjected to surgical interruption. Of these, six had excellent results, and five were completely relieved of pain but had persisting functional impairment and atrophy.

Grade III is the mildest form of the disease and the commonest. The onset is early but insidious; vasomotor changes occur early, and local edema is evident. The pain is mild and of a burning character. Motion is restricted. Surgery in these cases is rarely if ever indicated. If the disease is allowed to continue untreated, circulatory, trophic, and vasomotor changes occur. Dysfunction may be permanent. Procaine ganglion blocks is the therapy of choice. Betcher and Casten report 76 cases of this type clinically relieved by such therapy.

Summary

A case of reflex sympathetic dystrophy is reported.

A brief account of the etiology, physiology, and treatment is presented.

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Immature Vascular Nevi in Identical Twins

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While capillary nevi ("strawberry mark") are common in infants, they are very rare in identical (homologous, concordant, or uniovular) twins. The only authentic cases in the literature appear to be those by Tiedemann,[1] who reported two cases on the knees in 10-month twins, and Siemens,[2] whose patients had neck lesions. Cockayne [3] discussed the subject briefly but did not collect any cases.

Twins have been studied by geneticists to determine body constitution and the hereditary transmission of congenital defects and to evaluate the effect of intrauterine conditions. Although the literature is extensive, nothing is known regarding the cause of these abnormalities of the skin.

Identical twins originate from one ovum, are fertilized by one sperm, develop from a single placenta in a single chorionic sac, and possess identical genes. These identical genes are probably responsible for the similar site and type of vascular hypertrophy which occurred in the cases in this report.

It is interesting to note that, apart from vascular nevi, many dermatoses have been reported in identical twins of various age groups, including albinism, neurofibromatosis, xanthoma tuberosum, granuloma annulare, alopecia areata, disseminated lupus erythematosus, keloids, sarcoidosis, lipomatosis, atopic eczema, porphyria, epidermolysis bullosa, lichen pilaris, and Unna's nevus.

The etiology of vascular nevi in concordant twins is unknown, but numerous theoretical considerations have been advanced. Coincidence in my case can be excluded by the fact that identical areas are involved. Meirowsky [4] considered the site of a unilateral nevus to be determined by abnormal genes controlling the growth of a circumscribed area. It is doubtful that intrauterine factors (compression or placental defects) have any direct or indirect influence on their causation. Defects of the embryonic clefts are more likely factors in the development of linear or port-wine marks.

In a study of neoplasms in adult uniovular twins, Pastel and others [5] concluded that identical twins are more likely to develop tumors than multiovular twins and that the site, type of tumor, growth characteristics, and course were apt to be similar in both persons. Versluys [6] stressed the point that if one identical twin develops a tumor it is important to examine the other as soon as possible for evidence of a similar growth.

Report of a Case

Sara and Susan, identical twin girls, age 5-months, were examined by me in 1954 for similar raised hemangiomas over the right scapulae. The lesions were 1.5×1 cm., soft and compressible, and they had appeared within one week after birth. Sara's angioma was slightly deeper in the skin. No hereditary history was obtained. Although the mother was informed that the lesions would probably regress spontaneously, she insisted that therapy be instituted. A satisfactory result was obtained with the use of carbon dioxide snow.

Summary

A case of capillary nevus in identical twin girls is reported. The extreme rarity of the condition and the fact that the lesions occurred in identical sites are interesting.

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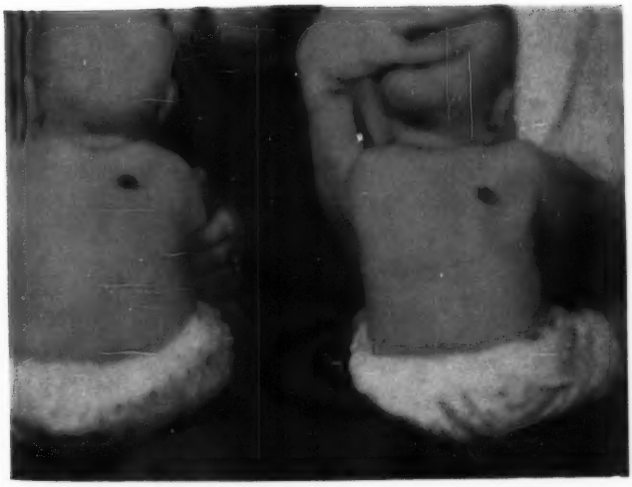

Immature vascular nevi in identical twins.

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Norwegian Scabies

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Severe hyperkeratinization characterizes Norwegian scabies, thus differentiating the condition morphologically from typical scabies. Thick crusted lesions composed of dried serum and keratin are riddled with furrows containing innumerable parasites and ova. The removal of a crust will reveal a moist reddened area with or without bleeding points. Patients may have diffuse papular eruptions and marked lichenification in areas not involved with crusts. Plaques may occur in multiple areas: the volar and dorsal aspects of the feet, the hands, the knees, the buttocks, the elbows, the penis, the wrists, the ears, beneath and around the nails, and over the brows. In general, sites of pressure or areas of skin stretching favor plaque formation.

Norwegian scabies, like typical scabies, appears to be an infestation with Sarcoptes scabiei var. hominis (Hering). Cutaneous peculiarities, hygiene, basal metabolic rate, hormone balance, and nutrition appear to be of little etiological significance in the natural history of Norwegian scabies.[1] The frequency with which Norwegian scabies is found in Mongolism and in mentally defective persons is noteworthy. The decrease in plasma vitamin A levels has been suggested as a possible contributing factor to the development of the hyperkeratinization seen in this rare condition.[1] Itching, formerly thought to be mild or absent, can be severe; however, the degree of itching varies considerably in a patient from time to time and appears to bear no relation to the degree of hyperkeratinization. Norwegian scabies can easily be misdiagnosed as psoriasis, keratoderma blennorrhagica, or other hyperkeratotic conditions.

Observations of two patients with Norwegian scabies form the basis of this report. One patient had been treated for generalized psoriasis for six years. The other patient had a presumptive diagnosis of lymphoma, and, before his final diagnosis was established, he infested other people with conventional scabies.

Report of Cases

CASE 1.—In 1943 a 24-year-old white man was admitted to a state mental institution with a diagnosis of low imbecile with Mongolism. His skin appeared normal. One year later he was hospitalized for scabies and furunculosis. The skin, including the scalp, was extensively involved. After one month's treatment with baths, hot compresses, and sulfur ointment he appeared cured.

In the spring of 1945 he was rehospitalized for treatment of malnutrition. At this time he received antiscabietic treatment.

The following spring he was hospitalized because of a scaly dermatosis. He was observed to scratch continuously during the day, but he slept well at night. On two successive days a "scabies ointment" was applied. He was discharged "improved" after two and one-half months.

In May, 1947, he was once more hospitalized for a dermatosis involving most of the body with thick scaly crusts over the hands and arms which fissured and bled. Treatment consisted of potassium permanganate baths, soothing lotions, vitamins, thyroid, sulfathiazole ointment, hydrous wool fat (lanolin), and mineral oil applications. Upon discharge two months later his skin was described as improved.

He was again hospitalized in 1951, and on several more admissions in the subsequent years he was treated for psoriasis. The dermatosis was described on various occasions as "generalized and involving the scalp" and "extensive and severe degree of psoriasis and secondary infection that involves almost his entire body." On his last admission, in February, 1956, for "chronic dermatitis quite typical of psoriasis" 50% of the glabrous skin and of the scalp was covered with crusts. The inguinal lymph nodes were greatly

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Fig. 1.—Foot and nail involvement.

enlarged. The rest of the physical examination was not remarkable. At this time the patient did not seem to scratch much or to complain of itching. Crusting was so severe that mobility of the knees was impaired. Treatment with coal tar ointment, ultraviolet light, ichthammol ointment, and daily baths with use of a soft brush to remove the scales improved his condition so that by July most of the crusting was limited to the buttocks, feet, and elbows. The remainder of the skin was markedly lichenified. In July, 1956, a portion of crust from the elbow was examined microscopically. Sarcoptes scabiei were found in abundance, and the diagnosis of Norwegian scabies was made.

Laboratory studies revealed normal urine; negative Kahn test; hemoglobin 10.4 gm., leukocyte count 13,000, with 1% eosinophils; serum cholesterol 221 mg. % (normal 98 mg. % to 250 mg. %); γ-globulin 2.4 gm. %. Two fasting serum analyses for carotene showed 214μg. % and 165μg. % (normal 60μg. % to 200μg. %), and the values for vitamin A were 71 and 170 I. U. % (normal is over 50 I. U. %).

Course and Treatment.—In an attempt to evaluate the antikeratinizing effect of vitamin A, all topical treatment except a daily soap bath was discontinued. The patient was given 150,000 units of vitamin A aqueous suspension daily by mouth. This experiment was discontinued after 14 days because of the extension and thickening of the encrusted areas (Fig. 1). A scaly area over the right brow developed into a thick hard plaque (Fig. 2), which when examined in serial sections microscopically showed numerous transected furrows and mites. The intervening papular and lichenified areas showed no change. The patient was then given an antiscabietic regimen consisting of a daily warm detergent bath to which was added 1 gal. of 3% hydrogen peroxide. The crusted lesions were gently removed and 1% γ-benzene hexachloride ointment* was applied to the entire body twice daily. Oral administration of 150,000 units vitamin A daily was continued. In one week there was marked improvement; by the second week the skin was practically clear, except for small areas on the soles. By the third week the skin was completely soft and smooth and treatment was discontinued. Fifteen months after treatment was discontinued the patient remained clear of any dermatitis. A biopsy specimen from the healed, formerly lichenified skin compared with a biopsy specimen from the same area taken at the height of his condition shows a marked reduction in the degree of lichenification (Figs. 3 and 4).

Case 2.—A 40-year-old white man had been committed to a state hospital for the previous seven years for treatment of chronic paranoid schizophrenia. In April, 1955, he was treated for "classical scabies"; further treatment was recommended which apparently he did not receive. In December of the same year, he developed a few crusted papular lesions on the thighs and penis which were considered typical of scabies, and he received a course of treatment with benzyl benzoate. A short time later scattered lesions on the penis,

* Kwell Ointment (Reed & Carnrick).

Fig. 2.—Silvery crusts over fingers and heaped-up plaque over brow.

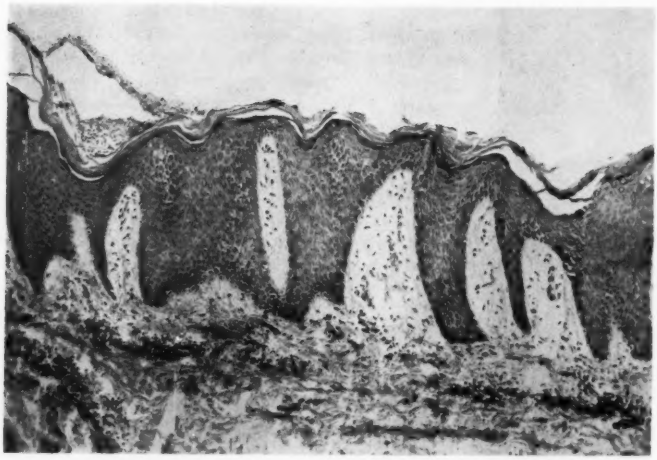

Fig. 3.—Microscopic section of lichenified nonscaly skin before treatment.

buttocks, and trunk were noted, and he was again treated for scabies. After two weeks he improved, but when seen one month later his lesions were extensive and secondarily infected, with regional adenopathy. He was given a course of penicillin injections and another course of benzyl benzoate applications. He was seen a few months later, and there was little to suggest any serious dermatologic problem. Within a few weeks, however, the patient developed a generalized, maculopapular, intensely itchy dermatitis of the trunk, extremities, buttocks, and penis. In a short time his lesions were markedly excoriated and resulted in widespread secondary infection, with oozing and crusting. He appeared chronically ill and undernourished. There was considerable adenopathy.

Despite treatment with antibiotics, antihistaminics, and wet compresses, he became progressively worse. Further therapy with prednisolone and corticotropin (ACTH) effected little change in his condition. The diagnoses considered were malignant lymphoma, exudative discoid and lichenoid chronic dermatosis of Sulzberger and Garbe, dermatitis herpetiformis, and pemphigus foliaceous. Findings on a skin biopsy taken in April revealed only chronic inflammation consistent with a lichenoid dermatosis. Blood studies disclosed no evidence to support the diagnosis of lymphoma. Steroid therapy was continued and, in addition, 4 mg. of reserpine was administered daily to control possible contributing psychogenic factors. The dermatitis became worse despite the above therapy. Findings on a second skin biopsy also failed to demonstrate any specific pathologic diagnosis. Because of the possibility of dermatitis herpetiformis, sulfapyridine was administered, without benefit. He was then transferred to the

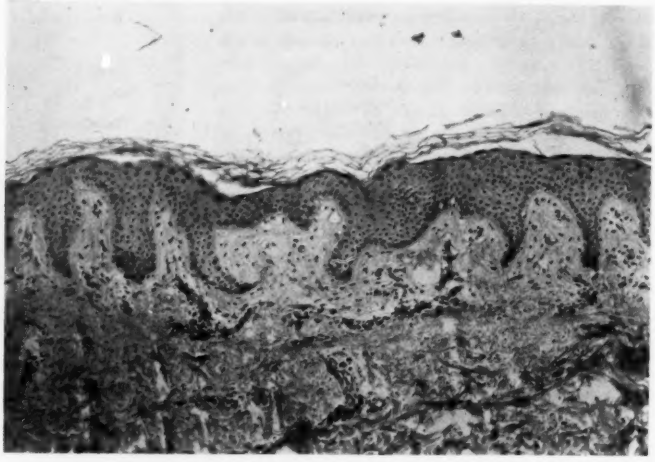

Fig. 4.—Microscopic section of same area as in Figure 3 after treatment, showing reduction in thickness of epidermis.

Herbert C. Moffitt-University of California Hospitals fo revaluation and treatment.

Physical Examination.—The general examinations.—The general examination revealed a well-developed, somewhat undernourished white man who appeared chronically ill. Positive findings were limited to a rubbery adenopathy in the axillae and groin and to the skin. The trunk showed erythematous, discrete and coalesced, flat-topped papules together with secondary changes of excoriation, lichenification, oozing, and infection. The extensor surfaces of the hands, forearms, and elbows and the interdigital web areas, the penis, and the dorsa of the feet were covered with heavy silvery-gray and yellow crusts.

The patient scratched a great deal of the time. A portion of crust was examined microscopically and revealed numerous Sarcoptes scabiei and ova, and the diagnosis of Norwegian scabies was made. Laboratory studies revealed normal urine; negative Kahn test; hemoglobin, 13.3 gm.; corrected erythrocyte sedimentation rate, 13 mm. in an hour, and a leukocyte count of 16,500, with 9% eosinophils. Fasting serum carotene was 174μg. %, and fasting serum vitamin A was 243 I. U. % (both high normal).

Course and Treatment.—Because of the excoriated and inflamed condition of his skin an attempt was first made to soothe the skin with starch baths before actually attacking the mites. Concurrently he received vitamin A, 50,000 units in aqueous suspension daily. The patient continued to scratch and excoriate his skin. He was, therefore, treated with 1% γ-benzene hexachloride ointment, which proved to be irritating and was discontinued. The itching became worse, and, despite the risk of irritation, soap and water baths were given to remove the mite-infested scales. Ten per cent crotamiton (*N*-ethyl-*o*-crotonotoluide) lotion† was applied to the skin after the bath. Administration of vitamin A was continued. Improvement was slow during the first two weeks, but very noticeable improvement occurred by the third week. The scaling became limited to a few small areas, and the remainder of the skin became less erythematous and much softer. One month after initiation of therapy he maintained his improvement and was then transferred back to the state hospital, where treatment was continued. The treatment consisted of a daily hot bath with a detergent, 50,000 units of vitamin A daily, and twice daily applications of crotamiton lotion. Three months later his skin was completely clear, and all treatment was discontinued. He was seen one year later, and his skin remained clear and had resumed its normal tone and texture.

† Ten per cent Eurax Lotion (Geigy Company, Inc.).

Comment

The role of vitamin A in the pathogenesis of Norwegian scabies is unknown. In contrast to two cases studied by Burks, Jung, and George [1] both patients in this instance showed adequate serum carotene and vitamin A levels. Vitamin A is known to exert an antikeratinizing effect on the skin; however, the administration of vitamin A is not necessary to clear the condition. As with certain other scaly and keratotic dermatitides, long-term therapy with vitamin A often proves to be a valuable therapeutic adjunct.

In Patient 1, an attempt to evaluate the antikeratinizing effect of vitamin A in aqueous suspension administered orally was unsuccessful. His condition progressed so rapidly, and he became so uncomfortable that after two weeks of this regimen antiscabietic therapy was instituted. Administration of 150,000 units of vitamin A was continued for a total of five weeks, until his skin was completely clear and had resumed its normal appearance and texture. The dermatitis of Patient 2 was more difficult to clear because his skin was so inflamed. He received 50,000 units of an aqueous suspension of vitamin A daily for four months, together with various soothing and antiscabietic regimens. It is noteworthy that they both showed renewed clinical evidence of scabies after a few weeks. Clinically do these represent reinfestations or treatment failures?

Twenty-one serial sections of a portion of lichenified nonhyperkeratotic skin over the back of Patient 1 failed to reveal anything suggestive of scabies but did demonstrate the marked thickening of the epidermis (Fig. 3). This lichenification is seen in many chronic skin irritations. When the source of irritation is removed (scratching? sensitization to the mites? [1]), the lichenification recedes and the epidermis approaches normal thickness (Fig. 4).

The frequency with which Norwegian scabies is seen in persons with Mongolism and in mentally defective persons is strik-

ing. One patient in the present report is a low imbecile with Mongolism.

The importance and difficulty in diagnosing Norwegian scabies is well illustrated by these two patients. Patient 1 was treated for psoriasis for six years. After this diagnosis was corrected to Norwegian scabies and appropriate therapy was instituted, his condition cleared completely within five weeks. Patient 2 was responsible for a small but serious intramural epidemic of conventional scabies.‡

‡ Approximately one month after Patient 2 was transferred to the Herbert C. Moffitt-University of California Hospitals the assistant head nurse on the ward, her husband, two psychiatrists, and their wives began to complain of severe nocturnal itching. (In primary infestation with scabies mites, itching and other signs caused by scratching may not appear until sufficient sensitization to cause irritation occurs; this may arise within a month or six weeks.[1,2,3]) All six persons developed tiny vesicles and papules over the extremities and the trunk. Microscopic examination of skin scrapings in one revealed Sarcoptes scabiei. As a prophylactic measure the entire ward, patients and personnel, were treated with crotamiton lotion. All the known cases of scabies responded promptly to treatment. The economic significance of this operation is evidenced by the cost of the medication, which amounted to $80.

Summary

Severe hyperkeratinization characterizes Norwegian scabies. The bizzare manifestations of Norwegian scabies can be easily mistaken for other conditions. Two patients with this condition are described. One had been treated for psoriasis for six years. The other was thought to have malignant lymphoma. Norwegian scabies is frequently seen in persons with Mongolism and in the mentally defective. The role of vitamin A in this hyperkeratotic condition remains obscure. Patients with Norwegian scabies can infest other persons with typical scabies.

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Acne Urticata Polycythemica

Report of a Case

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The cutaneous manifestations most frequently associated with polycythemia vera are a purplish-red discoloration of the skin and mucous membranes and ecchymoses particularly over the lower extremities. Both of these manifestations are readily understandable on the basis of the increase in total red cell volume characteristic of this disease.

In addition to these commoner cutaneous manifestations, acne urticata has been described in association with polycythemia vera more frequently than any other eruption. The term acne urticata was first used by Kaposi [1] to designate a chronic, severely pruritic eruption characterized by the development of pale red elevated wheal-like papules, ranging from the size of a pea to that of a small coin, surmounted by a vesicle with turbid contents. The vesicle or pustule is rapidly excoriated, and the surface of the papule becomes crusted. Involution occurs, with the formation of a delicate scar and hyperpigmentation. The eruption tends to appear in crops, with lesions first appearing on the face and later on the extremities, favoring the extensor surfaces, accompanied by severe pruritus and lasting for months or years. Kaposi's patients did not have polycythemia vera.

Acne urticata was first described in association with polycythemia vera by Werther [2,3] (1924), and the name acne urticata polycythemica was suggested by Pick and Kaznelson [4] (1925). There have been 14 cases reported in the literature.[2-15] These were comprehensively reviewed by Weidman and Klauder [11] (1939) and by Bluefarb [15] (1955).

The first recorded test for oxidase granules in the cellular infiltrate of acne urticata polycythemica was performed by Gans,[6] who reported the presence of a perivascular infiltrate composed of hyperplastic adventitial cells, neutrophilic and eosinophilic polymorphonuclear leukocytes, and oxidase-laden cells demonstrated by von Graff's oxidase test with naphthol blue as the reagent. The cells containing oxidase granules were of medium size, with a small nucleus and scanty cytoplasm. Weidman and Klauder [11] and Bluefarb [15] also demonstrated oxidase-laden cells in the cellular infiltrate of their cases stained vitally with benzidine with use of a method similar to Graham's method for histologic sections.

The purpose of this paper is to present an additional case of acne urticata polycythemica and to report the fourth case in which the presence of oxidase granules in the cellular infiltrate was demonstrated.

Report of Case

The patient, a 66-year-old Caucasian man, an unemployed laborer of Lithuanian birth, was admitted to the U. S. Naval Hospital, Philadelphia, on Oct. 7, 1957, complaining of a painful ulceration of one week's duration on the dorsum of his left great toe. The patient had enjoyed excellent health most of his life and had not been seen by a physician for over 40 years. Approximately three months prior to admission he had onset of a pruritic eruption characterized by vesicles becoming secondarily excoriated and crusted, starting on the forearms, spreading to involve the remainder of his body, but sparing his face, palms, soles,

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The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Services at large.

and middorsal back. During the week prior to admission, he noted several bullous lesions on the dorsal and lateral aspect of his feet which became denuded, leaving raw bleeding ulcerations. One such ulcer on the dorsum of the left great toe had become secondarily infected, causing the toe to become swollen, warm, red, tender, and painful on walking.

Examination on admission revealed a well-developed, fairly well-nourished elderly man, who walked with difficulty because of the painful ulceration on his left great toe and a tremendous bilateral scrotal hernia. His complexion was ruddy, with injection of his conjunctiva and mucous membranes. His lower extremities were of a dusky violaceous hue, with marked superficial venous congestion when in the dependent position. His vital signs were within normal limits, with his blood pressure 136/84. The chest was clear to auscultation and percussion. There was no cardiomegaly, and the heart sounds were of good quality and intensity, with no murmurs. The abdomen was soft and nontender, with the liver and spleen palpable 2 cm. below the right and left costal margins, respectively. No other organs or masses were felt. On the dorsum of the left great toe, there was a 2 cm. ulceration covered with a sanguineous crust and surrounded by a warm swollen erythematous tender zone. Elsewhere on the feet there were scattered bullous lesions and sanguineous ulcerations at the sites of former bullae on the dorsal and lateral surfaces of both feet. The skin was elsewhere involved in a generalized eruption (Fig. 1) sparing only the face, palms, and soles and partially sparing the middorsal back. The lesions consisted of erythematous macules, papules, excoriations, hemorrhagic crusted papules, pure vesicles and bullae on normal-appearing skin and pustules surmounting papules. There was superficial scarring at the site of former lesions, some of which were hyperpigmented. There was no significant lymphadenopathy, in spite of the obviously infected ulcer on the left great toe and the numerous lesions elsewhere on the body.

Fig. 1.—Acne urticata polycythemica, showing generalized eruption.

Laboratory studies on repeated blood cell counts revealed the hemoglobin to be 19 to 24.4 gm.; the red cell count, 6,060,000 to 7,660,000 and the hematocrit, 62 to 70 vol. %. The white cell count was between 12,100 and 22,250, with 75% segmented neutrophils, 1% band cells, 19% lymphocytes, and 5% eosinophils. The platelet count was 363,400. Blood volume studies with Cr^{51} revealed the total blood volume to be 8820 cc. (129 cc. per kilogram); the red cell volume, 6086 cc. (91 cc. per kilogram), and the plasma volume, 1734 cc. (26 cc. per kilogram). The arterial oxygen saturation was 100% after the breathing of 100% oxygen for five minutes. The preoxygenation sample was lost. The blood uric acid was 5.6 mg. %. Studies of the blood sugar, blood urea nitrogen, serum proteins, serum bilirubin, cephalin flocculation, and sulfobromophthalein retention were all within normal limits. A sternal marrow examination revealed a hyperplastic marrow with hyperplasia of all cellular elements. X-ray examination of the chest revealed prominence of the perivascular markings and hilar vasculature, with borderline enlargement of the cardiac silhouette and left ventricular prominence which was interpreted as consistent with the clinical finding of polycythemia. There was no evidence of intrinsic pulmonary or cardiovascular disease. An electrocardiogram was within normal limits. X-rays of the abdomen, barium enema, and intravenous pyelography failed to reveal any other abnormalities.

The patient was given oxytetracycline, 250 mg. every six hours, for the cellulitis of the left great toe, which responded rapidly over the first two weeks of hospitalization. He was given no specific therapy for his generalized eruption, which resolved spontaneously over the first two months of hospitalization, leaving superficial scars and hyperpigmentation. An occasional new bullous or vesicular lesion would develop on the forearms and feet, but such lesions remained rather evanescent. After two and one-half months of observation and study, the eruption had almost completely subsided, and it was elected to treat his polycythemia. He was bled a total of 3255 cc. in approximately 500 cc. increments from Dec. 24, 1957, to Jan. 18, 1958. There was marked improvement in the ruddy violaceous hue of the skin, but after 2230 cc. had been removed it was

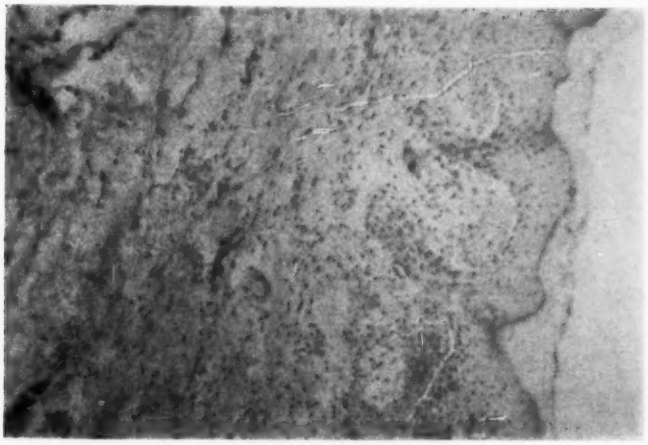

Fig. 2.—Biopsy of urticate papule, showing cellular infiltrate in section stained with hematoxylin and eosin. Reduced about 30% from mag. × 100.

observed that he was developing new lesions on the upper extremities, trunk, and face consisting of erythematous urticate papules 5 to 10 mm. in diameter with an occasional vesicular lesion surmounting the papule or arising on normal-appearing skin. The recurrent eruption subsided over the following two weeks with continued phlebotomy. On Jan. 27, 1958, he was given 5 mc. of P^{32} and discharged to his home. At the time of discharge he was free from his eruption, his hemoglobin was 17.4 gm., and his hematocrit reading was 57 vol. %.

Histologic Examination of Biopsy Material.—The initial biopsy was performed during the first week of hospitalization on a 2 mm. vesicular lesion appearing on normal skin from the dorsum of the right wrist. On microscopic examination the epidermis was relatively normal except for minimal hyperkeratosis without parakeratosis and exocytosis in scattered areas, with the infiltrating cells being predominantly eosinophils. The basal layer was disrupted by a vesicle which was, for the most part, subepidermal. The contents of the vesicle included many red blood cells, polymorphonuclear leukocytes, and eosinophils, much fibrin and degenerated epithelium, and a few lymphocytes. There was a moderate perivascular and periappendageal infiltrate in the upper dermis composed of round cells with varying-sized nuclei and of eosinophils. There was a number of spindle cells with pyknotic nuclei located perivascularly in the upper dermis, especially in the vicinity of the vesicle, and there was mild endothelial and adventitial proliferation of capillaries containing red blood cells.

A second biopsy (Fig. 2), of an urticate papule on the left forearm, was made during his recurrent eruption after he had been bled 2230 cc. This specimen had much the same histologic features as the initial biopsy specimen, with the notable absence of vesiculation. The epidermis was relatively normal. The upper dermis was moderately edematous, particularly at the dermoepidermal junction. There was a cellular infiltrate of eosinophils, polymorphonuclear leukocytes, and mononuclear cells with nuclei of various sizes throughout the upper dermis and papillae, being predominantly perivascular and periappendageal in location. A few thrombosed capillaries with fibrin and polymorphonuclear leukocytes were noted in the dermal papillae. Deep in the corium there was a light perivascular inflammatory infiltrate composed of eosinophils and large mononuclear cells.

A third biopsy was made at the time of the second on a lesion a few centimeters away having an identical clinical appearance. The urticate papule was injected intradermally with a freshly prepared, filtered, saturated solution of benzidine dihydrochloride in 0.2% hydrogen peroxide and 40% ethyl alcohol, according to the technique described by Weidman and Klauder.[11] The lesion developed a deep blue-black color within 3 minutes and was excised approximately 10 minutes after injection. Frozen sections were examined unstained and counterstained with Giemsa and with hematoxylin and eosin stains. The unstained section (Fig. 3) revealed a dense deposit of brown pigment in the upper dermis. On sections counterstained with hematoxylin and eosin, the brown pigment was seen to be both intra- and extracellular. The identity of the cells containing the peroxidase-positive material was uncertain because they were so heavily laden with the pigment. Some of the pigment appeared to be within the mononuclear wandering cells. The eosinophils were apparently obscured by the pigment granules, as none were recognizable on this section. On the section counterstained with Giemsa stain no mast

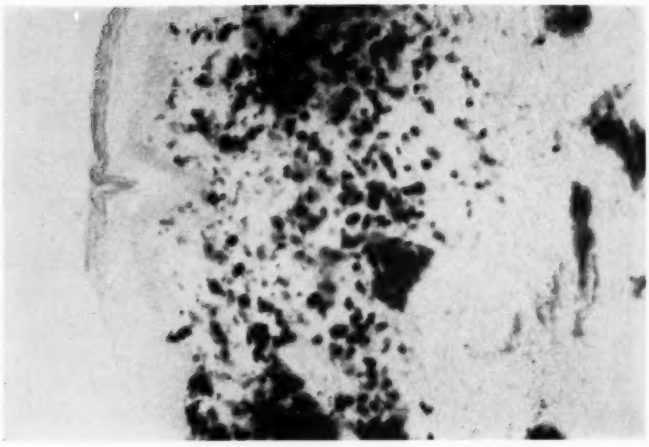

Fig. 3.—Biopsy of urticate papule vitally stained with benzidine without counterstain showing intense intra- and extracellular peroxidase reaction. Reduced about 30% from mag. × 100.

cells were found, and the eosinophils were again obscured by the heavy brown pigment.

Comment

The nature of the peroxidase-positive cells found in the dermis in acne urticata polycythemica and their significance remain obscure. Gans [6] reported that the oxidase-laden cells were of medium size, with a strikingly small round dark nucleus and scanty cytoplasm; however, the cells were so heavily laden with the oxidase-positive granules as to obscure the finer cellular detail. Weidman and Klauder,[11] using a somewhat different technique, described the peroxidase-positive cells tentatively as macrophages and speculated as to a possible autochthonous differentiation of the dermal macrophages in the direction of the myeloid series. They performed the peroxidase test on a case of acne urticata without polycythemia and were unable to demonstrate peroxidase-positive cells in the absence of polycythemia. Bluefarb [15] reported the presence of a positive oxidase reaction in his case but did not elaborate on the cellular detail of the lesion or of the peroxidase-positive cells.

In our case the peroxidase granules were found not only in the macrophages scattered throughout the dermis but were also found in the eosinophils, which were so heavily laden as to be obscured by the brown pigment in the vitally stained specimen, whereas they were numerous in the other biopsy specimens. This is not surprising, since the eosinophil is reported to have the strongest peroxidase activity among the polymorphonuclear leukocytes.[16] The explanation of the peroxidase activity in the macrophages of acne urticata polycythemica is not so easily understood. In our study of this patient, a normal subject was also injected with the benzidine solution as a control, and peroxidase granules were not demonstrable in normal skin. Further study is necessary to ascertain whether the peroxidase reaction is a constant finding in acne urticata polycythemica and to determine the significance of the peroxidase-positive macrophages found in the cellular infiltrate.

Summary

A case of acne urticata polycythemica is presented. Reference is made to 14 other cases in the world literature. The results of the benzidine peroxidase reaction in this case are reported, and comparison is made with the histologic findings in the three previously reported studies of the peroxidase reaction in acne urticata polycythemica.

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Philodendron as a Cause of Contact Dermatitis

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The current vogue involving the use of living plants for interior decoration and for patios, especially in the warmer areas, has resulted in the popularization of various species of philodendron and its close relatives. Instances of dermatitis from contact with such plants are not common, and yet they occur more frequently than is generally recognized, judging from references to this source of dermatitis venenata in dermatological literature.

The latest and most comprehensive dermatological texts either fail to mention philodendron entirely or give it scant attention. Andrews [1] listed philodendron among plants known to cause dermatitis but made no mention of the species involved. The latest edition of "Occupational Diseases of the Skin," by Schwartz, Tulipan, and Birmingham,[2] lists Philodendron consanguineum, and this species is also mentioned by Weber and by Pardo-Castello. Allen,[3] in discussing the poisonous and injurious plants of Panama, stated that Monstera deliciosa, which is a relative of philodendron with large, perforated leaves, is a source of contact dermatitis. He stated that "the juice of all species of monstera is acrid and caustic, causing a painful burning on contact with the skin, and that the juice of the leaves or stem will produce a skin rash in most individuals."

Harris [4] recorded the case of a woman who had dermatitis confined to the eyelids, apparently resulting from contact with philodendron vines in her home. Patch tests with all of the usual materials responsible for eyelid dermatitis, including cosmetics, were negative. A patch test with a leaf from one of the eight philodendron vines in the patient's home resulted in a strongly positive delayed reaction. The vines were said to be all of the same species, P. (scandens cardatum), probably intended to be *cordatum*. The dermatitis of the eyelids appeared

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Fig. 1.—Philodendron cordatum, a vine, commonly used as a house plant trained over a moss-covered stick.

about six months after she acquired the first of these plants, persisted with periodic exacerbations for four months, and disappeared when the plants were removed, although traces of the eruption persisted for another two months. There was apparently no eruption elsewhere on the body.

Pardo-Castello[5] gave a list of plants known to cause dermatitis, in which he included P. consanguineum, but he did not elaborate. Urbach and Gottlieb,[6] in "Allergy," in listing plants which have been reported to have produced a dermatitis mentioned Philodendron without identifying the species or making further comment. Weber,[7] in a list of cutaneous irritants, mentioned, without discussion, P. consanguineum.

During the past few years we have observed at least 12 patients who have developed contact dermatitis resembling the type of eruption seen in poison oak dermatitis from exposure to several species of philodendron.

The genus Philodendron ("tree-loving") is one of approximately 100 genera in the family Araceae,[8] which includes such plants as the common calla lily, and most members of this family come from tropical areas. The family is characterized by flowers which have a central fleshy columnar portion, or spadix, subtended by a large bract, or spathe. Some members of this family have been used for medicinal purposes, and some are edible, such as the root of the taro, from which poi is made by native Hawaiians, and the *ripe* fruit of M. deliciosa. The leaves of some members of this family are violently irritating if they get into the mouth, notably Dieffenbachia seguine, which causes painful and alarming swelling of the mouth, tongue, and throat.

There are approximately 100 species of the genus Philodendron, a number of which are in common use, notably P. cordatum, with small, heart-shaped, glossy leaves, which is a vine and is grown indoors as a pot or container plant often trained over a moss-covered stick. P. selloum is another currently popular plant, usually grown out-of-doors in warm climates in patios or roof gardens or in front of buildings. It has large, divided leaves and tends to grow in a mound. A number of other species of philodendron have recently been introduced.

Report of Cases

CASE 1.—The subject was a 45-year-old man, a building inspector. The eruption began about two weeks prior to visit. There was a history of previous attacks of a similar eruption during the previous 10 years, and the patient knew that he was sensitive to poison oak, although there was no history of recent exposure to poison oak. Just before the onset of his present eruption the patient had inspected a downtown office building which had a roof garden where many plants, including philodendron vines, were growing. The patient stated that he had walked among these plants and had come into close contact with them.

Examination disclosed an erythematovesicular eruption, with crusting, arranged in blotches and streaks and involving the dorsal aspects of the hands and all aspects of the forearms. Patch tests were made with plants to which the patient had been exposed, including philodendron (species not identified), English ivy and two other types of ivy, and primula (species not identified). All of the tests were strongly positive except that for primula sensitivity, which was negative. The case was considered to be of occupational origin.

CASE 2.—The subject was a 50-year-old housewife. The present attack began two days prior to visit. There had been recurring attacks on the arms during the previous three years. The patient was known to be sensitive to rubber. She had been exposed to various plants at home, including philodendron. There was no known exposure to poison oak. A patch test to a philodendron leaf (probably P. cordatum) was strongly positive, with a delayed reaction. Patch tests to eight other plants, including Primula obconica, were all negative. The patient stated that she had polished the leaves of the philodendron vine with olive oil several days before the onset of her eruption.

Examination showed that the eruption was mostly on the flexor aspect of the left forearm and consisted of an irregular palm-sized area of erythema, swelling, vesicles, and blebs arranged in blotches and streaks. There was also a swollen and less severely affected area on the outer aspect of the left thigh.

CASE 3.—The subject was a housewife. The present eruption began six days prior to visit. There was no known exposure to poison oak. The patient had previously had an eruption in the axilla

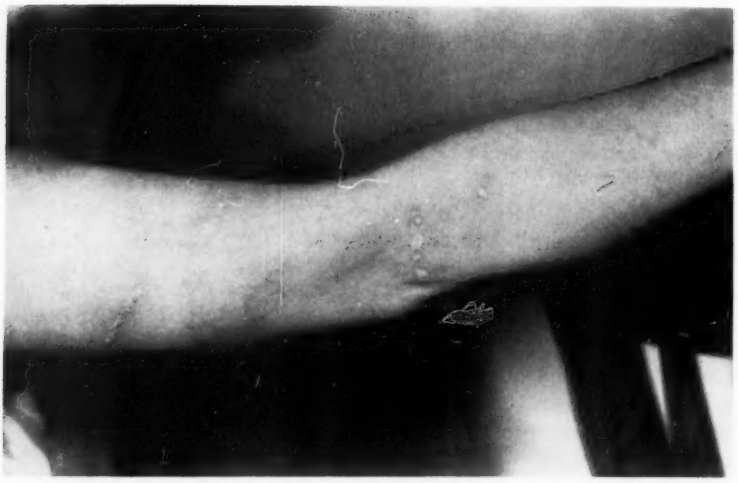

Fig. 2 (Case 3).—Erythematovesicular eruption in blotches and streaks, covered with calamine lotion and resembling dermatitis from poison oak or poison ivy.

from rubber dress shields, to which she was found to be sensitive. The patient had had contact with P. cordatum and with primula (species unidentified). A patch test with philodendron leaf was strongly positive in 48 hours. The primula was not tested.

Examination revealed an acute erythematous and vesicular eruption in blotches and streaks on the arms, dorsum of the right hand, and thighs and legs.

Case 4.—The subject was a 42-year-old housewife. The patient had had scattered eruptions at intervals for 16 months. She had had contact with philodendron and other plants. A patch test with a philodendron leaf was strongly positive. Patch tests with English ivy and "grape ivy" were negative.

Examination showed an erythematous, moist, eczematized eruption on the dorsal aspects of the hands, in the axillae, on the thighs, and elsewhere. The patient also had seborrheic dermatitis of the scalp, ears, and umbilicus.

Case 5.—The subject was a 32-year-old woman, a secretary at a large seed company. She had had an eruption of the right hand at intervals for four or five years. Finally, careful and repeated questioning revealed that the patient had P. cordatum vines at the office, where she frequently watered them or picked off dead leaves. Patch tests with the leaf of P. cordatum was strongly positive. Many other patch tests were negative.

The eruption involved the right hand, especially all aspects of the fingers, and was ill-defined, erythematous, and slightly vesicular.

Case 6.—The subject was a 43-year-old woman, a hospital ward clerk. She had had recurrent eruptions of the hands for about five years. The present attack was of one week's duration and consisted of an ill-defined, blotchy, erythematovesicular eruption involving the hands, fingers, and forearms, especially the flexor aspect of the left forearm near the wrist and cubital area. The patient had had a philodendron vine in her home for about 10 years. A patch test with philodendron leaf resulted in a 3+ reaction.

Case 7.—The subject was a 31-year-old housewife. The present eruption was of one week's duration, and there was a history of many previous similar attacks. The patient stated that she had carried some alfalfa hay in contact with her arms prior to the attack. She also had two philodendron vines in the house. The flexor aspects of the wrists were involved with an erythematovesicular eruption in blotches and streaks, strongly suggestive of a plant dermatitis. A patch test with alfalfa hay was negative. A patch test with a leaf of the patient's P. cordatum resulted in a strongly positive reaction in 48 hours which was still strongly positive after a week.

Case 8.—The subject was a 53-year-old woman, a secretary. The present eruption was of five days' duration, was confined to the radial and flexor aspects of the left forearm, and consisted of an erythematous and vesicular eruption arranged in blotches and streaks, characteristic of a plant dermatitis. The patient had a number of house plants. Patch test of a philodendron leaf (probably P. cordatum) was strongly positive. Patch tests with three other plants were negative.

Case 9.—The subject was a 53-year-old man, a bank clerk. The present acute attack was of one

week's duration, and there was a history of many previous attacks over a period of eight years. The eruption involved all aspects of the hands and forearms, with erythema and vesicles in blotches and streaks.

The patient had two house plants, P. selloum and M. deliciosa, which he handled occasionally. A patch test with the philodendron gave a strongly positive delayed reaction which was still strongly positive after two weeks. A patch test with monstera leaf was negative.

CASE 10.—The subject was a 48-year-old housewife. The eruption began about one week previous to visit. She had had contact with philodendron vine and English ivy at home. The eruption involved the back of the right hand and the flexor aspect of the right forearm and consisted of an acute erythematovesicular eruption, typical of a plant dermatitis. A patch test with English ivy was negative. There was a strongly positive delayed reaction to a patch test with a philodendron leaf (probably P. cordatum).

CASE 11.—The subject was a 48-year-old man, an office worker. The eruption began three or four days prior to the visit and involved the flexor aspect of the left forearm with a dime-sized group of closely crowded vesicles surrounded by erythema. There were three similar patches on the right forearm and abdomen. The patient had several house plants, including two species of philodendron. A patch test to P. cordatum was negative, but a leaf of P. speciosum gave a strongly positive reaction.

CASE 12.—The subject was a 45-year-old housewife. The eruption began about one week prior to visit, and she had had two similar attacks during the preceding six to eight weeks. The patient had worked in her garden and also had a philodendron vine in the house. The eruption was scattered over the extensor aspects of the forearms and on the legs and consisted of irregular erythematovesicular lesions with a tendency to occur in blotches and streaks. Patch tests were made with leaves of five plants which the patient had handled, including three weeds, lantana, and P. cordatum. The last resulted in a strongly positive reaction with vesiculation; the lantana gave a moderately positive reaction, and the three weeds gave only slightly positive reactions.

Summary and Comment

Contact dermatitis from philodendron vines has received scant mention in current dermatological texts and in dermatological literature.

The incidence of dermatitis from these plants is not great, but dermatitis occurs more frequently than is generally realized.

In view of the present vogue of utilizing these plants for interior decoration and patio planting, the opportunity for exposure has been greatly enhanced.

A series of 12 patients with contact dermatitis from several species of philodendron, especially Philodendron cordatum, is presented.

The usefulness of philodendrons for ornamental planting should not be impaired by the occasional case of contact dermatitis, but the possibility of such a source of eruptions should be considered in any dermatitis, especially of the hands and arms, suggestive of an external origin.

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Addendum

Shortly after this report was submitted for publication, an article appeared in *California Medicine* 88:329 (April) 1958 by Clete Dorsey, M.D., reporting an instance of contact dermatitis from Philodendron cordatum in the case of a young woman employed in a commercial nursery who had frequent contacts with plants of this species.

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Cutaneous Xanthomas

A Reappraisal of Their Significance

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Xanthomas have been known to man for centuries and their clinical description was recorded by Thomas Addison in 1848,[1] long before modern medical diagnostic techniques were evolved. Accordingly, our understanding of xanthomas resulted chiefly through observation of minute morphological differences in lesions, the recording of various distributional patterns, and the occasional detection of some associated state such as jaundice, diabetes, or a familial tendency. A relatively complex terminology resulted, i. e. xanthoma disseminatum, xanthoma diabeticorum, biliary xanthomatosis, etc. This nomenclature frequently did not reflect distinguishing morphological characteristics among various xanthomatous lesions but merely reflected differences of associated conditions in individual patients and histories. The growth of physiological chemistry and the development of modern serum analytic techniques has largely replaced the need for such a complex morphological approach and has rendered much of this traditional terminology obsolescent.

Morphology

Xanthomas are circumscribed dermal infiltrations of cholesterol or triglyceride which appear as yellowish-to-orange-to-red lesions with a shiny appearance which range in size from pinpoint papules to nodules of several centimeters in diameter. Clinically three basic types of xanthoma are seen: First are *plane* xanthomas, which are seen most frequently about the eyes and in this location are known as xanthelasmas. The second are the *tuberous* xanthomas. These occur with greatest frequency about the extensor prominences. Third, are the *papular* xanthomas which may be seen anywhere but most commonly are found on the buttocks, on the trunk (especially the anterior axillary folds), and on the palms. Often those papular lesions found on the palmar surface localize in the skin creases. They have, in this location, been included with tendon xanthomas although this term should be reserved for the infrequent situation in which xanthomatous infiltrates actually occur within tendon sheaths. The histopathology of xanthomas has been completely covered in works by Thannhauser [2] and Lever,[3] and a restatement would serve no useful purpose.

Etiology

An appreciation of the various possible causes of xanthomas is chiefly the result of studies of Thannhauser [2] and Lever and his colleagues.[3,4] A modification of the table originally proposed by Thannhauser appears below. It should be noted that this table lists the possible causes of xanthomas rather than disorders of lipid metabolism. Consequently, those disorders which do not result in the appearance of xanthomas are not included.

It will be noted that chronic pancreatitis no longer appears as a cause of hyperlipemia. Klatskin and Gordon [5] and Lever [4] have recently shown that pancreatitis is probably an effect rather than a cause of hyperlipemia. The underlying disorder is in most cases an idiopathic hyperlipemia. Similarly, from recent observation of two cases,[6] it has become my suspicion that mild diabetes mellitus is only rarely, if ever, the cause of hyperli-

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Department of Dermatology, University of Oklahoma School of Medicine.

TABLE 1.—*Causes of Cutaneous Xanthomas*

I. Hyperlipemia
  A. Essential (familial) hyperlipemia
    (1) Children (Bürger-Grütz disease)
    (2) Adults (with or without pancreatitis)
  B. Secondary to:
    (1) Renal disease
      (*a*) Lipoid nephrosis
      (*b*) Glomerulonephritis
      (*c*) Lupus erythematosus
    (2) Diabetes mellitus
    (3) Glycogen storage disease
II. Hypercholesteremia
  A. Essential (familial) hypercholesterenia
  B. Secondary to:
    (1) Biliary obstruction
      (*a*) Operative
      (*b*) Cirrhosis
      (*c*) Hemochromatosis
    (2) Hypothyroidism
    (3) Hand-Christian syndrome
III. Localized tissue accumulations
  A. Inflammatory
  B. Neoplastic
    (1) Nevoxanthoendothelioma (juvenile)
    (2) Reticulohistiocytic granuloma
    (3) Other tumors
  C. Hereditary or traumatic

pemia. Rather it may be that in most instances the relationship of diabetes to hyperlipemia is aggravative and coincident rather than causal. A genetic link between the two conditions may exist.

A knowledge of the significance of xanthomas may be acquired only by chemical analysis of the fasting serum. In view of the often conflicting statements in the authoritative texts regarding the importance of a diagnosis of xanthomas, it was decided to examine by modern biochemical techniques a series of patients with various types of xanthomas.

Data

A study was made of 20 patients, at the University of Michigan and the University of Oklahoma, whose presenting complaint was that of xanthomatosis, either plane, tuberous, papular, or combinations thereof. In all instances, the investigation of these patients included a determination of fasting serum cholesterol and total lipid.* At least one biopsy was performed in each case. Patients with either tuberous or papular lesions had hepatic and renal evaluations, cardiovascular studies, and chest x-rays. All patients had complete physical examinations and histories. Careful family

* Serum lipid determinations were accomplished in the Biochemical Section, Department of Dermatology, University of Michigan; the Cardiovascular Section, Oklahoma Medical Research Foundation, and the University of Oklahoma Medical Center Clinical Laboratories.

TABLE 2.—*Findings in Twenty Patients with Xanthomas*

Patient	Age	Sex	Xanthoma			Serum	TFA, Mg. %	Cholesterol Mg. %	Electrophoretic Abnormality	Family Hx	Diagnosis †
			Xanthelasma	Tuberous	Papular						
1-6	45	4-F 2-M	+	—	—	Clear	<900	<300	No	3 with Xanthelasma	Xanthelasma
7.A	56	M	+	—	—	Clear	720	725	Yes	Neg.	A-S
8.K	54	F	+	—	—	Clear	410	405	Yes	HC *	HC
9.B	31	M	—	+	+	Cloudy	2,137	560	Yes	Coronary	HL
10.Y	19	F	+	+	—	Clear	470	429	Yes	HC	HC
11.B	50	M	—	+	—	Clear	870	570	Yes	Neg.	A-S, HC
12.L	34	M	—	—	+	Cloudy	23,372	2,344	Yes	Neg.	HL
13.H	30	M	—	+	+	Cloudy	1,440	385	Yes	Coronary	HL
14.R	58	M	—	+	—	Clear	488	480	Yes	Neg.	A-S, HC
15.S	54	M	—	+	—	Clear	465	510	Yes	Neg.	HC
16.S	60	M	+	+	—	Clear	820	466	Yes	Neg.	A-S, HC
17.A	55	M	—	+	+	Clear	1,280	275	Yes	Neg.	DM, HL
18.B	53	M	—	+	+	Cloudy	4,240	475	Yes	Neg.	DM, HL
19.B	19	M	—	—	+	Cloudy	2,300	630	—	Neg.	LE (nephrosis), HL
20.K	30	M	—	—	+	Clear	732	568	—	Neg.	Myxedema, HL

* HC=hypercholesteremia
† A-S=arteriosclerosis; HL=hyperlipemia; DM=diabetes mellitus; LE=lupus erythematosus.

histories were taken, and, when indicated, key members of the family were interviewed and examined and their serum was analyzed. The results obtained in this series appear in Table 2.

Comment

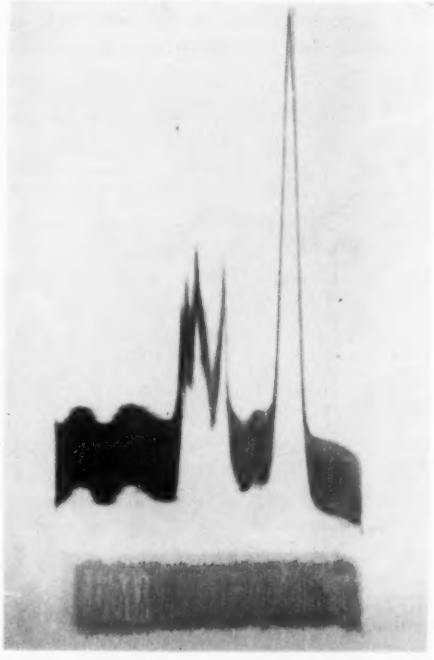
In regard to the significance of the xanthomas seen, it is apparent that the group divides itself into two obvious sections: those patients with plane xanthomas about the eyes (xanthelasmas), who were without other lesions, and those patients having tuberous or papular xanthomas, with or without xanthelasma. Of those eight patients with only xanthelasmas, two had abnormal serum lipids. These patients had mild cholesterol elevations, one with an associated arteriosclerosis. In four of the eight patients, there was a family history of xanthelasma. Thus, while it is apparent that the presence of xanthelasmas may be associated with an underlying lipid disorder on occasion, in the majority of these patients there was no serum lipid abnormality. It is concluded that xanthelasmas alone, occasionally but not frequently, are associated with systemic metabolic disease.

Quite the reverse is true of tuberous or papular xanthomas of the skin. All twelve patients had metabolic disease. Of those nine with *tuberous* lesions, eight were males. In four, a diagnosis of hyperlipemia was made. Two of these patients had associated diabetes mellitus. Five of those with tuberous lesions had hypercholesteremia. Three of these had associated arteriosclerosis. One had a familial history of xanthomas. Of the three patients with only *papular* lesions, all were males and one had primary hyperlipemia. Two had secondary hyperlipemia due to nephrosis in one instance and to myxedema in the other. In general, papular lesions were seen in those patients with the highest serum lipid levels regardless of the etiology. No patients with tuberous or papular xanthomas had normal serum lipid values.

It has been alleged that simple inspection of the serum will serve to differentiate patients with hyperlipemia from those with hypercholesteremia, but this is not invariably true. In Case 17, the patient had a clear serum but was suffering from hyperlipemia. In the course of following these patients under treatment, we have observed[7] repeatedly that when serum total lipid levels fall below 1350 to 1400 mg. %, the serum may be free of visible turbidity. Thus, it is probable that patients with hyperlipemia of mild degree (1000 to 1300 mg. % total fat) often go undiagnosed when only inspection of the serum and determination of serum cholesterol are made. The determination of serum cholesterol is not a sufficient screening test since, in hyperlipemia, the cholesterol may be either normal or elevated. The cholesterol varies from patient to patient with the level of total serum lipid.

Free-moving-boundary electrophoresis was performed on the serums of all but two patients. In each case there were abnormalities when the serum lipid levels were

Fig. 1.—Representative electrophoretic pattern in idiopathic hyperlipemia.



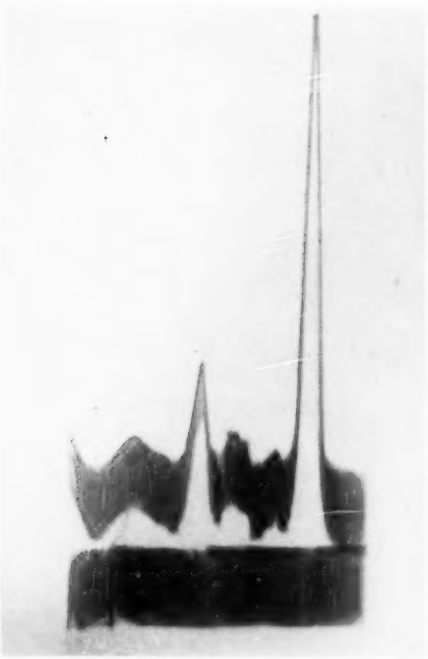


Fig. 2.—Representative electrophoretic pattern in familial hypercholesteremia.

elevated. Usually, elevations in the α_2-β area were seen in hyperlipemia, and there was often an associated lowered α_1. In hypercholesteremia, simple β elevations were usually seen. Similar findings have been reported by Lever.[8] Typical pattern tracings are seen in Figures 1 and 2. In the primary forms of hypercholesteremia and hyperlipemia, these electrophoretic pattern changes often persisted to a less degree even after the serum lipid levels returned to normal.

Conclusions

From this study of 20 patients with xanthomas, the following conclusions were drawn:

1. Abnormalities of serum lipids can be demonstrated in all patients with papular or tuberous xanthomas. Some of the patients with only xanthelasma will also have metabolic disease.

2. The nature of the underlying metabolic state cannot be diagnosed by inspection of the xanthomas. However, in general, papular lesions are seen with higher blood lipid levels and papular lesions are rarely seen in women. When seen in women, they nearly always accompany hypercholesteremia rather than hyperlipemia.

3. The underlying abnormality can be demonstrated only by obtaining an evaluation of both total cholesterol and total blood lipid. Not all patients with hyperlipemia have cloudy serum or elevated cholesterol.

4. Abnormal electrophoretic patterns often accompany the serum lipid abnormalities. These patterns are frequently characteristic.

5. Thorough investigation of patients with xanthomas to identify an underlying metabolic abnormality is important, because these disorders often have an unfavorable prognosis which can, at times, be altered by appropriate therapy if instituted early in the course of the disease.

Summary

Twenty patients with cutaneous xanthomas of varied types were thoroughly investigated for underlying disease. The high incidence of serum lipid pathology revealed emphasizes the need for careful study of each and every patient with xanthomas.

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The Appearance of Lips of Suckling Infants

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During the period of nipple feeding, infants have certain temporary anatomic configurations of the cheeks and lips that appear to be aids in sucking. One textbook on pediatrics [1] makes mention of a fullness of the cheeks on both the buccal mucous and the skin surface that is produced by excess of adipose tissue. The term sucking pads has been applied to these accumulations of fat. Another structure well-known to pediatricians [1-3] is a whitish tumefaction in the center of the upper lip which is called the labial tubercle (see Figures). To one who is not familiar with this formation, it may, when well developed, appear to be a blister and may, on this account, cause alarm that a burn or some other trauma had recently been suffered. Perhaps a queer cheilitis or even a lymphangioma might be considered by some in a differential diagnosis of what is deemed to be abnormal. The labial tubercle is none of these things; it is a soft, boggy structure that serves a purpose and disappears as do the "sucking pads" when the need for exerting strong negative pressure in sucking upon nipples is over.

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Dermatologic textbooks, even those devoted to skin diseases of children, make no mention of these interesting, though normal, phenomena. Our purpose in this communication is to draw attention to them and to note further the condition of the rest of the surface of the lips of sucklings. In addition to the labial tubercle, one can see on the vermilion of the upper lip two smaller wing-like elevations flanking it, and there is more of the same sort of thing in a single continuous band on the entire lower lip (see Figures). These formations, too, may upon casual inspection suggest bullae in their tumid whiteness. Like the labial tubercle they are soft and, moreover, are topographically rugose. Alternating ridges and furrows traverse them roughly in their short axes. During nursing the furrows deepen and the ridges become more prominent. They resemble the scorings on the jaws of a vise or pliers which prevent slip.

Fig. 1.—Clinical aspect of the labial tubercle and the wing-like elevations flanking it on the upper lip, and the grooved swelling of the entire lower lip. Note the fullness of the cheeks caused by the sucking pads.

Fig. 2.—Compare with Figure 1. Note the general similarity of all features.

Between feedings they recede somewhat. Desquamation sometimes occurs. In time, after weaning, sucking pads, labial tubercle, and the rest disappear, and the usual appearance of lips supervenes.

No doubt the sum of these arrangements enhances the power to hold a nipple firmly in the mouth and to produce strong suction. One may speculate on what is the structural basis of these labial swellings. We would guess that there is hypertrophy of epithelium and underlying tissues of the lips and probably "laudable" edema that is intensified by sucking during nursing. The edema may at times be so intense as actually to cause some blister-like separation of epithelial strata. Ultimately, both hypertrophy and edema, if these should be underlying, recede completely. We know of no microscopic studies to substantiate these conjectures. Of course, biopsy could not justifiably be done on living subjects, but histologic examination could be made on infants who had died and were being autopsied for other reasons. If the process should be mainly edema, postmortem examination would probably reveal little or nothing, but if there is hypertrophy of tissues then a difference from the usual would, again probably, be readable.

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Granuloma Pyogenicum

Differential Diagnosis

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Granuloma pyogenicum is a term introduced by Hartzell,[1] in 1904, to describe a benign human tumor occurring on skin and mucous membranes.

The etiology of this tumor is not fully established, though trauma and infection with pyogenic bacteria are frequently associated. Michelson[2] reported a history of preceding trauma in 50% of the cases in his series, and Crocker[3] defined granuloma pyogenicum as "a fungating tumor produced by pus cocci."

These lesions are well described in the literature.[4] They occur at all ages and equally distributed between the sexes. The preferred sites are hands, feet, lips, face, upper part of trunk, and umbilical regions on the skin and the buccal, nasal, laryngeal, vaginal, and cervical mucosae. During gestation, they occur on oral mucosa frequently enough to have been given the special title of pregnancy tumor.[5]

They present as vascular tumors, bright red to brownish-red, pedunculated or sessile, with smooth or frambesiform surface (Figs. 1, 2, and 3). They are firm and do not compress readily, and they are essentially nontender and nonpainful. Ready bleeding and suppuration are characteristic, and accompanying lymphangitis, lymphadenitis, and fever may be found. Usually their size is about 1 cm., but they grow to 4 or 6 cm. The onset of growth is insidious. There follows a rapid increase to maximum size; then growth stops, and the lesion persists this way indefinitely with no self-healing tendency. Crocker[3] described

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Fig. 1.—Lesion of one month's duration on the right upper eyelid of a 39-year-old woman. This depicts a typical simple granuloma pyogenicum.

a half-walnut-sized granuloma pyogenicum, excised after being present four years.

The histopathology is characteristic. It may be described readily by assuming that large blood vessels grow up from the dermis through a narrow neck or pedicle into a nodule filled with loose connective tissue and covered with thin or thickened epidermis and that these vessels then divide and subdivide like branches from a tree trunk, forming lobules or clusters of small dilated blood vessels imbedded in loose connective tissue.

Epidermal changes include atrophy, acanthosis and hyperkeratosis, and erosion. In the dermis around the blood vessels, inflammatory-cell infiltrate may be marked or nearly absent. Some degree of proliferation of endothelial cells without lumen formation occurs fairly constantly (Figs. 4, 5, and 6).

Histopathology usually permits an unequivocal diagnosis of this tumor. Occasionally, however, its microscopic differentiation from other benign or malignant

Fig. 2.—This 59-year-old man had a lesion of six weeks' duration on the right side of the internasal septum at the choana. This is typical simple granuloma pyogenicum also.

vessel-element new growths can be very difficult.

The historical background of granuloma pyogenicum is of interest because of the intense controversy concerning its etiology. At the Congress of Surgery in Paris in 1897, Poncet and Dor [6] described a new entity that they called human botryomycosis. Clinically, the lesions of the entity were neoplastic fungating ulcerative granulomata, developing from the dermis by a thin pedicle, at times to be visualized only with traction. They believed that this growth was caused by a parasite, Botryomyces, that grew in clusters in tissues. The clusters aggregated to form yellow grains, visible to the naked eye. On the basis of microscopic study, they believed that the parasite could be found in great abundance in zones of disintegration at the periphery. However, cultures of Botryomyces from these lesions had all the characteristics of Staphylococcus pyogenes, and the parasite could be distinguished from the pus organism only by animal inoculation, which reproduced the tumor experimentally. Some time before, in 1879, Rivolta had described certain mulberry-like tumors occurring on the spermatic cord of horses after castration, and in 1887 Bollinger named the disorder botryomycosis, since it was caused by a parasite, Botryomyces, characterized by a tendency to grow in clusters (reviewed in Wile's article [7]).

Poncet and Dor, after describing four cases, claimed that their entity was the same as Bollinger's botryomycosis. The delineation of a new pathologic entity, as well as

Fig. 3.—Myxosarcoma of the skin in a 65-year-old man with lesion of the nasal choana area. (Reprinted from Knerler and Rowe,[20] A. M. A. ARCH. DERMAT.) This lesion later metastasized to lung.

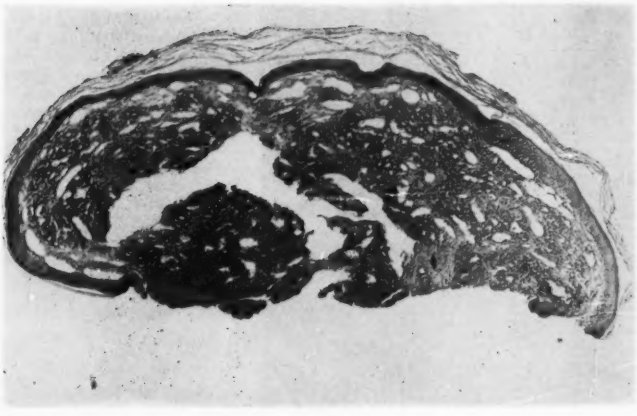

Fig. 4.—Section of a vascular growth beneath the left eye of a 19-month-old girl. The nodular nature of the specimen is clearly seen. There is moderate hyperkeratosis, with thinning of epidermis and absence of rete ridges. The dermis is filled with dilated blood vessels in clusters and close-packed endothelial cells embedded in loose connective tissue. Large vascular spaces near the narrowed base and smaller vessels in clusters peripherally are typical. Inflammatory cells are not in evidence.

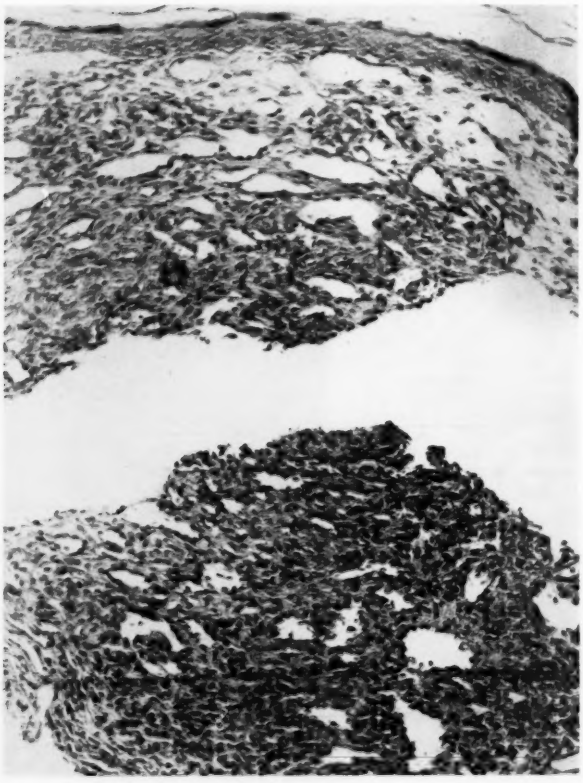

Fig. 5.—Higher-power view of portion of Figure 4.

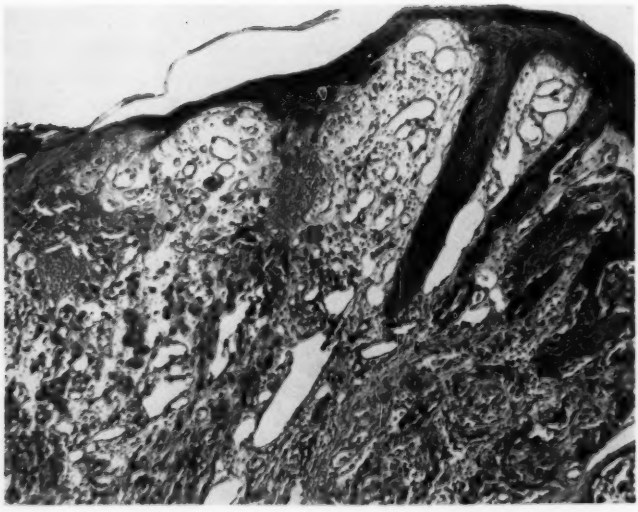

Fig. 6.—Malignant melanoma from the back of a 16-year-old boy. The clinical diagnosis was granuloma pyogenicum. The lobulated appearance, with clusters of dilated vessels and edema in the upper dermis, and larger vessel spaces in the midcutis give indication of why this lesion would resemble granuloma pyogenicum clinically. On both sides, melanoma cells are much in evidence.

the alleged identity of its etiologic agent with Botryomyces of horses, stimulated great interest in Europe. As a result, many investigations were undertaken and many articles were published.

After careful study, Bodin,[8] in 1902, concluded that the organism involved here was Staphylococcus pyogenes var. aureus and that in all probability Poncet and Dor's Botryomyces was S. pyogenes var. aureus. Also in 1902, Carriere and Potel[9] introduced a diversion by describing two cases in which they believed they could trace a connection of the pedicle of this new entity to underlying sweat glands, and hence assumed it was a fibroadenoma of sweat glands.

In 1904 Hartzell[1] presented a literature review on the subject and reported that Poncet had agreed in the interim that the mulberry-like masses in the tissues were nothing more than heaps of cells which had undergone a special type of degeneration. Hartzell described his four cases, in which he found no evidence to substantiate Carriere and Potel's theory, and introduced the term granuloma pyogenicum.

In 1910 Lenormont[10] also reviewed the literature, wrote a careful study of his own on the subject, and concluded that Poncet and Dor had indeed described an entity but that it was not the same as botryomycosis of horses and that its etiology was unknown, though trauma and infection played a part.

In 1910 Wile[7] published on granuloma pyogenicum, with a review of the European and American literature. His conclusions were essentially those of Lenormont, and he believed that S. pyogenes var. aureus was a large factor in the etiology.

Thus, by 1910, the controversy about the etiology of granuloma pyogenicum had subsided. This controversy had served to steal some of the limelight from the clinical importance of the disorder, which lay principally in its essentially malignant appearance and "its absolutely constant benign nature," to quote Lenormont.[10]

Initially Poncet and Dor described this entity as neoplastic fungating ulcerating granulomata. Crocker[3] defined it as a fungating tumor produced by cocci. Finally, in 1917, Montgomery and Culver[11] graphically delineated the clinical interest in granuloma pyogenicum with the following statement: "The red, granular, easily bleeding tumor simulates so forcibly what one is accustomed to regard as a malignant growth, and the condition in reality is so benign, and its recognition as an innocent tumor becomes so easy and so definite when its pathology and symptoms are remembered, that these facts alone make its separate consideration most advantageous."

A literature review reveals references to the consideration of granuloma pyogenicum from this point of view.

Crocker[3] described one case of this entity, of four years' duration, excised as a sarcoma. Kreibich[12] described one case mistaken for melanosarcoma, on an index finger. Heuck[13] discussed the clinical differentiation from Kaposi's hemorrhagic sarcoma. Michelson's paper[2] included a clinical picture of a granuloma pyogenicum that simulated a cutaneous horn. He stated that some granuloma pyogenicum were "flat sessile lesions looking surprisingly like a chancre," that granuloma pyogenicum of the lower lip may be mistaken for an epithelioma, and that angioma, angiosarcoma, and hemangioendothelioma must be considered in the differential diagnosis. Eller[14] mentioned resemblance to the tuberous form of bromoderma. Behrman[15] published a picture of a scalp lesion with the caption "Granuloma pyogenicum. Large tumor clinically suggestive of nevocarcinoma." Allen[5] published a clinical picture also, with the title "Ulcerated granuloma pyogenicum of arm resembling an aggressive cancer."

Thus, a granuloma pyogenicum may have a clinical resemblance to a sarcoma, a benign or malignant angioma, an epithelioma, or a melanoma. It is unlikely that lesions with appearance so malignant will be treat-

ed casually and escape biopsy with eventual recognition.

However, with granuloma pyogenicum so firmly established as benign, patients with lesions which are this entity clinically, if these lesions are small and nonaggressive, may not fare so well. This is especially so since thorough curettage and desiccation is usually completely adequate therapy for granuloma pyogenicum.

There are references in the literature to both benign and malignant conditions that simulated a simple granuloma pyogenicum. Wansker, Smith, and Olansky,[16] describing adenoacanthoma of skin, a dyskeratotic squamous-cell carcinoma with tubular and alveolar formation, showed a photograph of such a lesion and stated, "The initial impression was that the lesion represented a pyogenic granuloma, although a malignant melanoma and squamous cell carcinoma were also considered."

Levan[17] presented a patient at the Los Angeles Dermatological Society meeting in January, 1958, with a lesion on the left side of the neck that strongly suggested a granuloma pyogenicum clinically but which was most likely a clear-cell hidradenoma from microscopic study.

At the Clinico-Pathologic Conference of the American Academy of Dermatology and Syphilology[18] meeting in Chicago, December, 1957, the four cases following were studied and are of interest in this connection.

Spiller and Knox showed a 1 cm. tumor on the plantar surface of a toe which was granuloma pyogenicum clinically but an eccrine poroma (Pinkus) actually. Cawley stated in discussion of his case of milkers' nodule that the lesion bore a strong resemblance to granuloma pyogenicum clinically. Winer presented a case with angiomatous lesions that occurred singly, with the gross appearance of granuloma pyogenicum, which was most likely Kaposi's hemorrhagic sarcoma. Weidman, in his comment on one of Beerman's cases, wrote, "The sections point up the high degree of vascularity which prompted the clinical impression of pyogenic granuloma." The microscopic diagnoses offered here were glomus tumor, sweat gland tumor, and epithelial tumor.

I[19] reported that seborrheic keratoses with pseudoepitheliomatous hyperplasia (Weidman) may be granuloma-pyogenicum-like clinically and resemble a prickle-cell carcinoma microscopically.

Finally, Knerler and Rowe,[20] discussing myxosarcoma of skin, showed a picture of this lesion (Fig. 3) bearing a marked resemblance to granuloma pyogenicum.

In order to evaluate further the need for biopsy in lesions clinically granuloma pyogenicum, our pathological records were surveyed for the years 1953 to 1957, inclusive. During this five-year period, 59,737 specimens were submitted for biopsy from all the services.

In this material, there were 124 sections in which the clinical diagnosis had been granuloma pyogenicum, and microscopic diagnosis was not in accord in 47 of these—about 38%. The various microscopic diagnoses made in these 47 cases which were clinically granuloma pyogenicum are listed below.

Acute and chronic inflammation	7
Folliculitis	1
Scar	3
Epidermal cyst	2
Subepidermal fibrosis	3
Xanthoma	1
Verruca vulgaris	4
Molluscum contagiosum	1
Angioma	4
Glomus tumor	1
Seborrheic keratosis	1
Seborrheic keratosis with pseudoepitheliomatous hyperplasia (Weidman), as described by Rowe[19]	3
Keratoacanthoma	1
Intraepidermal carcinoma	2
Prickle-cell carcinoma	1
Skin-appendage tumor	2
Basal-cell carcinoma	4
Dermal nevus	2
Junction nevus	1
Juvenile melanoma	2
Melanoma	1

Thus, including the above with information from the literature, 17 tumors, both benign and malignant, and 11 other disorders may be, or may have been, misdiagnosed as granuloma pyogenicum clinically.

Summary and Conclusion

Granuloma pyogenicum is a benign human tumor occurring on skin and mucous membranes. Not infrequently it takes on a bizarre clinical appearance suggestive of malignancy. Such lesions are most likely to be subjected to microscopic study and their true benign nature ascertained.

However, a small nonaggressive innocent-looking vascular tumor that strongly resembles a granuloma pyogenicum clinically may be one of a fairly large number of other skin disorders or tumors, some benign and some malignant. Many such instances are incidentally described in the literature and are found in the records of our pathology department. Therefore, any lesion that resembles granuloma pyogenicum should have this clinical impression confirmed by biopsy.

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Oral Treatment of Keloids

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There have been many different methods of treatment for keloids. The fact that new methods are being sought constantly is evidence of their relative inadequacy. Some years ago it was suggested to us that systemic administration of redox-active substances might have an effect on keloids. The following report deals with experiences in 45 consecutive cases seen in the Dermatologic Out-Patient Clinic of Receiving Hospital.

Material and Methods

The use of tetrahydroxyquinone (THQ) was suggested by Mr. James V. Sheridan, working at that time at the Detroit Institute of Cancer Research.* This substance had been tested in animals and had been found free of toxic effects. It was fed by us to 20 female rats in doses ranging from 10 mg. per day to 180 mg. per day per rat for periods up to eight months. No harmful effects were observed. The animals gained weight regularly, and microscopic examination of internal organs showed no significant pathologic changes. In the early phases of the work, THQ was supplied by Mr. Sheridan in the form of gelatin capsules containing 30 mg. of the dry substance triturated with inositol. Later, THQ made in the laboratories of the Paul B. Elder Company was supplied by Mr. Howard E. Parker, of that company, in similar capsules, mixed with cornstarch. Doses for patients varied from 30 mg. to 180 mg. daily.

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*William L. Simpson, Ph.D., M.D., Scientific Director.

In order to rule out spontaneous regressive changes in hypertrophic scars, no keloids of less than six months' duration were included in the study. Many patients had had their keloids for several years. The oldest case had large lesions of 40 years' duration. Repeated biopsies were made in some cases, and a fairly large material of surgically removed keloids was studied for comparison. No other therapy was administered.

Clinical Results

There was some favorable influence in every case. This was usually manifested first by a lessening of tension and of the pain and pruritus so often associated with keloids. Objective regression of lesions was slow but definite. In long-standing cases, partial involution continued at a slow rate over several years. Younger lesions tended to respond more rapidly, and in three cases, involution was complete. The keloids became softer to palpation. Three large and old lesions discharged a white cheesy substance at intervals. The area of the scar did not become smaller and remained visible even though it became soft and level with the surrounding skin. Some lesions continued to regress after the withdrawal of the drug. There has been no recrudescence during the time of observation, which in some cases is now five years.

Five representative case histories follow.

CASE 1.—A Negro woman, age 75, had keloids on the chest, back, abdomen, and arms for 40 years. There was no history of injury. The lesions were large and lobulated, some measuring 6 in. in diameter and having a height of 1 in. Surgical removal of keloids had resulted in keloidal scars on two different occasions. The lesions were very pruritic, and scratching resulted in secondary infection at times. Treatment was started with THQ, 30 mg. three times a day, in August, 1954. In two months, partial involution of keloids was obvious. The regression was slow. The patient continued to take THQ daily except when she was

Fig. 1 (Case 1).—Right half of the back. *A*, photograph taken in May, 1954. *B*, photograph taken in January, 1958. This was the patient having very large keloids of 40 years' duration. Regression obviously was slow and incomplete. Moreover, it is difficult to bring out the differences in thickness and consistency in a photograph. Comparison of the regions indicated by arrows provides an impression of the regression in size and the softening of the tense and succulent lobes of keloids shown in *A*.

treated for a nose and throat ailment for three months. Her highest dose has been 180 mg. daily. The lesions have regressed slowly until at the time of writing her largest lesion is 3½ in. in diameter and the height has decreased more than 50% (Fig. 1).

Case 2.—A Negro woman, age 36, had keloids in the intermammary fold extending onto the breasts and measuring 3 to 4 in. in the largest diameter. Between the breasts the lesion was 1½ to 2 in. thick. There was a keloid on the flexor surface of the right arm ½ in. high and 6 to 8 in. long. A lesion on the back was 2 in. in diameter and ¾ in. in height. Duration was 10 to 12 years. The patient started taking THQ, 30 mg. a day, in August, 1954. The dose was raised gradually to 180 mg. daily. All lesions regressed slowly but definitely. The lesions between the breasts responded more slowly, and there were frequent bouts of drainage. Culture of exudate showed nonpathogenic organisms of the normal skin flora. The lesion on the back has diminished to ⅛ in. height at the time of writing. The lesion on the arm has regressed proportionately. Therapy is being continued. No untoward symptoms have arisen.

Case 3.—A Negro woman, age 27, had 12 keloids on the mammae, over her back, and on legs and arms. The lesions were ½ to 1½ in. in diameter. They were on the average ½ in. high. This person was a definite keloid-former. Her treatment was interrupted frequently. Starting in 1954, she would attend the clinic for three or four months at weekly intervals and then disappear for several months. Therapy was started with a dosage of 30 mg. daily, which was then raised to 90 mg. daily. Involution began after two months and has continued at a rather steady rate in spite of the irregularity of treatment. Now most lesions are raised but slightly above the surface, and their diameter is considerably reduced.

Case 4.—A Negro girl, age 8, had suffered second- and third-degree burns at the head, neck, trunk, and extremities. She showed keloid formation at graft sites, donor sites, and places of deep burns and was unable to extend her arms because of keloidal scars. Therapy was begun six months after the accident. She was given 30 mg. of THQ twice daily, then three times a day. The keloids at the donor sites involuted very rapidly in two months; the grafts showed involution, though not complete, in the same length of time. She was able to extend the arms partially to the point where she could dress herself and comb her hair in six months. The large lesions on the face were smaller and softer in six months.

Case 5.—A Negro boy, age 4, lacerated his arm in November, 1953. He was first seen in June, 1954, with a keloid at the site of laceration 1½ in. long, ¼ in. high, and ½ in. wide. He was given 15 mg. of THQ daily. Involution was rapid. A buried suture came to the surface and was removed in August of the same year. The patient was discharged in November, 1954, with the scar completely flattened.

Histologic Observations

Histopathologic changes were followed in several cases by repeated biopsy. In addition, sections of a considerable number of untreated keloids were studied. Tissues were fixed in 10% formalin or in formol-alcohol, and paraffin sections were stained by seven different procedures as follows: hematoxylin and eosin, acid orcein and Giemsa, thionine, toluidine blue, periodic acid-Schiff (PAS), Mallory connective tissue, and Gomori reticulum stains.

Examination of untreated keloids reveals a rather uniform picture. The epidermis shows no significant changes. The papillary layer of the dermis appears normal. The collagen bundles are thin and wavy; there are fixed tissue cells but not in abundance; there may or may not be evidence of reticulum at the dermoepidermal junction; mast cells are present in moderate numbers;

the tissue does not stain metachromatically with basic dyes and usually is PAS-negative. The keloid is evident in the upper two-thirds of the reticular layer. The collagen bundles are coarse, sometimes hyalinized and sometimes frayed. Thick bundles stain with a mixture of red and blue in Mallory sections. There is no encapsulation. Fixed tissue cells are few. There is a moderate number of mast cells. This area stains metachromatically and is PAS positive. There are no appendages present, these having been pushed to the side. There is no elastic tissue present. Reticulum in small amounts may be seen around the blood vessels.

By comparison, sections taken from six months to four and one-half years after the start of therapy were reviewed. Treatment was seen to produce definite changes in the collagen, reticulum, mast cells, fixed tissue cells, and melanocytes. There were differences in metachromasia and PAS positivity in both digested and undigested specimens.

In earlier sections (Figs. 2*A*, 3*A*, and 4*A*), the collagen bundles appear to be breaking up. The coarse bundles are less dense but many retain a red tinge with the Mallory stain (Fig. 3*A*). The changes are more pronounced in the two-and-one-half-year specimen (Figs. 2*B*, 3*B*, and 4*B*). Coarse bundles are fewer in number, and those that remain are frayed and the fibers are very wavy. They stain a pure blue with Mallory's mixture (Fig. 3*B*). The fixed connective tissue cells show a relative or actual increase in number (Fig. 3*B*). The reticulum fibers become more evident as the collagen bundles decrease in size. Reticulum is seen mainly around the blood vessels in Figure 4*A*. In Figure 4*B* a fish-net-like appearance of reticulum fibers is seen throughout the sections; many of the coarse bundles seem to consist of reticulin rather than mature collagen.

The metachromasia apparently decreases under therapy, while positive staining with the PAS procedure increases as treatment progresses. This is evident in the tumor portion of the section. Mast cells are increased in number, especially those with PAS-positive granules. After digestion with diastase, the positive stain of the connective tissue remains constant, but the mast-cell granules either disappear or become much lighter.

The melanocytes appear to increase in size and seem to have more numerous and larger dendrites.

In Case 1, a biopsy was performed 18 months after institution of therapy; another one, after treatment had been interrupted for 4 months. The first section showed numerous large and well-granulated mast cells scattered diffusely in the tissue. Metachromasia of the ground substance was reduced. The second specimen showed a smaller number of mast cells with fewer granules than before. Some metachromatic granules were seen free in the section. The metachromasia of the ground substance seemed more pronounced, though unevenly distributed.

The drug appears to affect the keloids only. Sections of normal skin away from the vicinity of the keloid show no change. Skin from which the keloid has regressed shows the changes described earlier as occurring in keloids.

Comment

X-ray and surgery have been the standby in the treatment of keloids for years. Cornbleet [1] felt that surgery was more effective after the lesions had been infiltrated with hyaluronidase several times. Stritzler [2] presented a case bearing out this contention. Gathings [3] infiltrated the keloid with liver factor "S" in sterile aqueous solution (Kutapressin) and hyaluronidase, thereby rendering it more amenable to surgery. Ronchese and Kern [4] state that the satisfactory surgical removal of keloids was enhanced by the oral administration or the injection of corticosteroids. Asboe-Hansen et al.[5] reported good results following the local infiltration of hydrocortisone acetate.

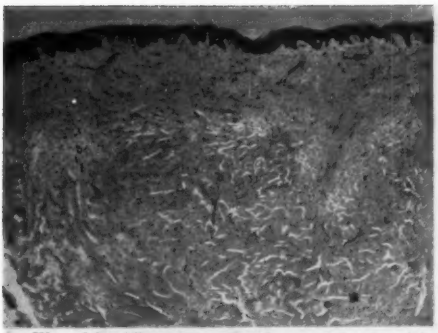

Fig. 2A (Case 1).—Sections stained with hematoxylin and eosin; × 30. A, keloid after six months of treatment. Thick and partly hyalinized collagen bundles in the pars reticularis of the corium.

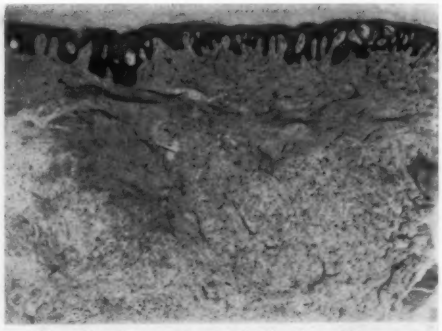

Fig. 2B (Case 1).—Keloid after 33 months of treatment. Epidermis thicker, probably owing to shrinkage of underlying tissue. Collagen bundles thinner and less eosinophilic. Larger number of connective tissue cells.

Fig. 3A (Case 1).—Sections stained with Mallory's trichrome stain; × 135. Collagen bundles after six months of treatment show frayed edges; retain red tinge in center.

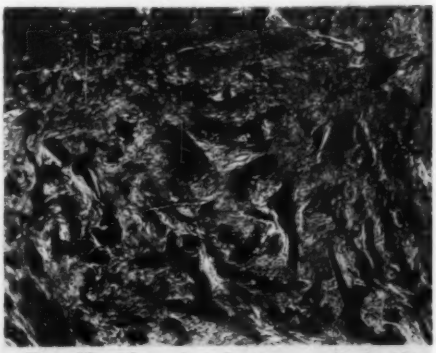

Fig. 3B (Case 1).—Sections stained with Mallory's trichrome stain; × 135. Collagen after 33 months of treatment stains pure blue. There are relatively few thick bundles. There are many thin wavy fibers and numerous connective tissue cells.

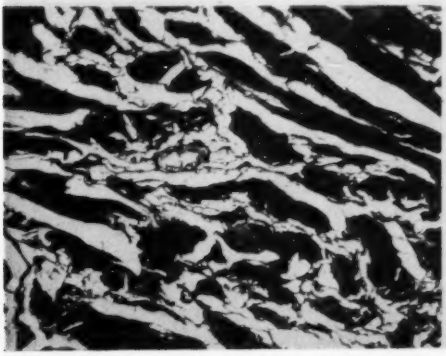

Fig. 4A (Case 1).—Sections impregnated with Gomori's reticulum stain; × 280. After six months of treatment there are many thick collagen bundles.

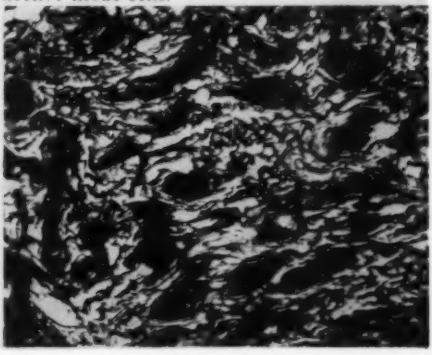

Fig. 4B (Case 1).—Sections impregnated with Gomori's reticulum stain; × 280. After 33 months of treatment, most bundles are broken up into wavy fibers, many of which are argyrophilic.

Later, they[6] reported atrophy of normal skin surrounding the keloid.

None of these measures is ideal as far as therapeutic results are concerned. They are not applicable in all cases, especially not in widespread spontaneous keloids or those resulting from extensive burns. Some, such as the corticosteroids or x-ray therapy, may have serious side-effects or sequelae. A form of systemic therapy that does not have the drawbacks of the corticosteroids and avoids the disagreeable features and shortcomings of local injections, surgery, or irradiation would be highly desirable.

The oral treatment with tetrahydroxyquinone leaves much to be desired. It is tedious and slow in action, and its effect is incomplete in large keloids. It has, however, caused some regression in keloids of up to 40 years' duration and has completely resolved some younger lesions. It relieves the pain and pruritus so often associated with keloids rather promptly. No side-effects or untoward reaction have been observed, and the drug has proved nontoxic in animal experiments using comparatively tremendous doses. The only undesirable reaction encountered has been occasional local breakdown of keloid tissue accompanied by the discharge of necrotic material. This occurrence apparently is due to the softening of the tissue around old devitalized collagen bundles and actually is a sign of effectiveness of the treatment.

Of equal interest are the effects of THQ on connective tissue as seen under the microscope.

The evaluation of the changes found histopathologically is difficult; for example, the increase in the reticulum is difficult to estimate. When a section of fetal skin is stained for reticulum and compared with a treated keloid, the similarity is evident. Also the number and relationship of the fixed tissue cells bear some similarity. Both features are common where young connective tissue is laid down. In treated keloids, on the other hand, old connective tissue seems to disappear. The collagen in the regressing keloid is very wavy, similar to fetal collagen. The mast cells, however, are poorly developed in fetal skin, while they are numerous and well granulated in the treated keloid.

It was mentioned that treated lesions are softer on palpation. Softening also is evident in the greater ease with which local anesthetics can be injected into treated keloids. These changes are manifested histologically by a regression of the collagen, the presence of more fixed tissue cells, and an increase in mast cells. That the latter play a role in the formation of ground substance was postulated by Asboe-Hansen.[7] Changes in the ground substance are indicated in our sections by a decrease of metachromasia and increased reactivity to the PAS agent. Changes of this type are due to desulfation, according to Mowry.[8] Differences in polymerization or dissociation between polysaccharides and proteins also may be responsible.

The action of THQ is selective. Biopsy specimens from the normal skin of persons under treatment with THQ showed none of the changes seen in the treated keloid. This observation raises the question of what it is in the keloid that this medication controls. Alteration of redox potentials in the tissue is a possibility. Action on enzyme systems seems another one. The enzymes of the dermis have not been studied to any great extent by histochemical means. β-Glucuronidase has been found in normal cutis by Campbell[9] and Montagna.[10] Alkaline phosphatase has been demonstrated in keloids by Kopf.[11] In a few preliminary studies we saw esterase-positive granules in mast cells. It appears worth while to investigate possible changes occurring in these enzymes during treatment.

Summary

Four years of experience with tetrahydroxyquinone (THQ) as an oral treatment for keloids suggest (1) that keloids of all ages show some response to this drug, (2) that more complete regression is obtained

in younger keloids, (3) that there are definite changes in all the elements of the dermis, (4) that THQ is selective in its action, and (5) that the effect of THQ may be mediated by enzymatic action.

Wayne State University College of Medicine (7).

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Recurrent Iododerma

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Cutaneous allergy due to iodide ingestion is so varied that practically every type of lesion has been reported as a sensitivity reaction to iodide.[1] This case report is concerned with an unusual morphologic variant, namely, ulcerative and carbuncular lesions, and also with the comparison of results of therapy with and without corticotropin in two separate episodes of iododerma in the same person.

Carey and his collaborators[2] reported successful treatment with corticotropin of a patient with an extensive bullous erythema multiforme and angioneurotic edema. Fourteen days after discontinuance of penicillin and on the twenty-third day of administration of hydriodic acid syrup, the patient developed the eruption. Prompt beneficial response occurred following administration of corticotropin, with relapse following its discontinuance and with improvement again on its reintroduction. While the sequence of events would appear to show favorable effect of therapy, the etiologic agent (penicillin or iodide) was not clearly established. Aquilina and Bissell[3] reported the effectiveness of treatment with hydrocortisone systemically and locally in a case of granulomatous fungating lesions following the ingestion of iodides. They stressed the importance of local steroid (hydrocortisone) therapy in the eventual cure and emphasized that a recurrence of lesions after discontinuance of systemic treatment healed with the reintroduction of local hydrocortisone treatment alone. Since hydrocortisone given systemically was administered in saline infusions, the possible therapeutic effect of chloride should be considered.[4] Theodos[5] and Park et al.[6] in separate reports were able to accomplish bronchography with an iodine-containing contrast medium in an iodine-sensitive person and prevent urticarial manifestations of iodism by prophylactic administration of corticotropin. Cape[7] reported treatment with potassium iodide of a patient who had acute and chronic pulmonary disease, with subsequent development of fungating facial lesions and eosinophilia. When his condition became critical, he was given corticotropin intravenously (85 mg. total in eight days) with apparent acceleration of his over-all recovery. The facial lesions were reported to regress slowly, but the healing time was not given. The author questioned whether such small doses could have influenced the outcome even though administered by intravenous drip.

There may be some hesitancy concerning the use of steroid hormones in carbuncular and ulcerative lesions, since these hormones reputedly inhibit walling off of inflammatory lesions. The report of Wright and Greco,[8] who successfully employed this modality in the treatment of pyoderma gangrenosum, is contrary to this opinion. Since iododerma is potentially serious and may even be fatal,[9-13] this possible risk in the use of corticotropin seemed justifiable in the following case. The use of corticotropin has not previously been reported in carbuncular and ulcerative lesions due to iodide.

Report of a Case

A 67-year-old Negro man was admitted to the Veterans' Administration Center Hospital, Kecoughtan, Va., on Dec. 10, 1956, with chief complaints of a "black out spell," bilateral chest pain, cough, and wheezing.

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From Medical Service, Veterans' Administration Center, Kecoughtan, Va.; Consultant in Dermatology (Dr. Pariser).

Significant physical findings were as follows: Temperature 99 F, pulse rate, 130, blood pressure 140/92, increased breath sounds and moist rales over the right lower chest posteriorly, and moderate wasting of the muscles of the hands. Appropriate laboratory studies were normal. Chest x-rays were interpreted as normal. (Frequent examinations of the sputum for acid-fast bacilli had been negative on previous admissions.)

Diagnoses of acute and chronic pulmonary disease, arteriosclerotic heart disease, and progressive muscular atrophy of the upper extremities were made. On previous hospitalization he had had folliculitis of the face, a carbuncle of the neck, a furuncle of the buttock, and a nondermatologic reaction to phenylbutazone (Butazolidin) given for the treatment of arthritis. Iodides had not been administered prior to these pyodermic episodes.

Initial treatment consisted of pentaerythritol tetranitrate (Peritrate), aminophylline, and tetracycline. One tablet of Quadrinal * was prescribed four times daily, beginning Dec. 14, because of persistent cough and wheezing.

On Dec. 20, a small erythematous papulovesicle appeared on the left posterolateral thoracic wall. This became umbilicated and progressed rapidly to a large tender erythematous nodule with central ulceration covered with a purulent exudate (Fig. 1). In addition, the patient complained of sore throat and hoarseness on Dec. 28. Examination revealed slight reddening of the pharynx.

* Each tablet of Quadrinal (Bilhuber-Knoll Corporation) contains ephedrine hydrochloride, 0.025 gm.; theophylline-calcium salicylate, 0.130 gm.; phenobarbital, 0.025 gm.; potassium iodide, 0.324 gm.

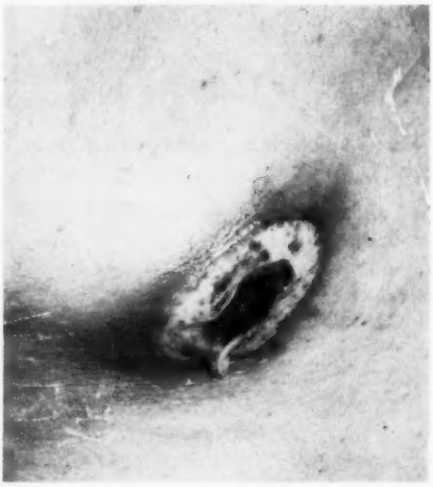

Fig. 1.—Initial ulcer on the posterolateral chest.

Punch biopsy of this skin lesion (Figs. 2 and 3) revealed intact epithelium, spotty distribution of vacuolized cells, moderate infiltration of neutrophils in the epidermis, and almost complete absence of papillae. The corium adjacent to the epidermis stained strongly with eosin, while the remaining corium stained slightly and showed intense edema. The corium was infiltrated with neutrophils, a moderate number of eosinophils, and histiocytes. These latter cells often had large nuclei, distinct nuclear membranes, and large nucleoli. Cells were occasionally multinucleated. Small arterioles showed fibrinoid changes, and a small vessel, probably a vein, was completely necrotic and surrounded by a collar of proliferative and swollen

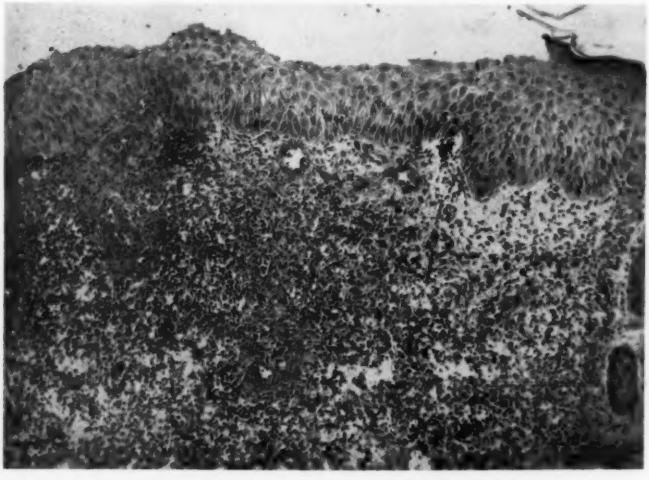

Fig. 2.—Skin biopsy specimen from posterolateral ulcer; × 120.

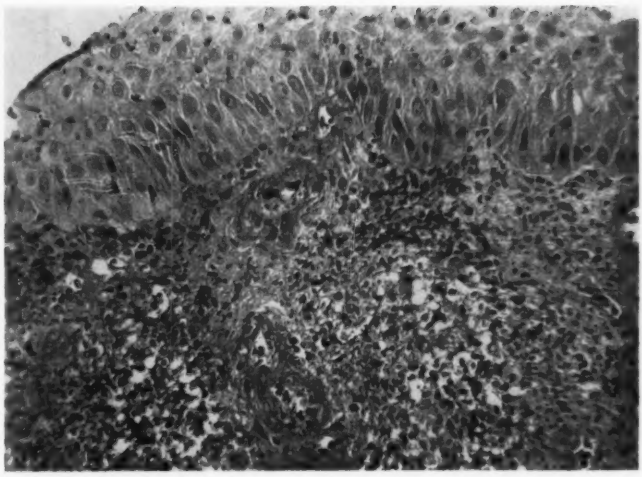

Fig. 3.—Greater magnification of specimen in Figure 2; × 220.

histiocytes, neutrophils, and lymphocytes. These changes were felt to be compatible with a hypersensitivity reaction and with iododerma.

Cultures on two occasions for bacteria and on one occasion for fungi were negative. Treatment consisted of erythromycin, 500 mg. orally every six hours, an antibiotic ointment, Neosporin ointment,† and saline soaks locally. These failed to alter the progressive course. The possibility of a reaction to iodide was considered, and Quadrinal was discontinued on Dec. 28. All other medications were continued. The lesion began to regress and was epithelized (healed) in 31 days (Fig. 4). Because the chronic cough persisted, ammonium chloride cough mixture ‡ was prescribed on Feb. 19. On Feb. 25, lesions appeared on the posterior neck, the sternal region, and the left lower anterolateral chest. These lesions very promptly assumed

† Neosporin ointment (Burroughs-Wellcome & Co., Inc.). Each gram contains polymyxin B sulfate, 5000 units; bacitracin, 400 units; neomycin sulfate, 5.0 mg.

‡ Ammonium chloride cough mixture, U. S. P. Each dram contains potassium iodide, 0.060 gm.; ammonium chloride, 0.32 gm.; ammonium carbonate, 0.089 gm.; ethyl nitrite spirit, 0.060 gm.; glycyrrhiza fluidextract, 0.2 ml.; camphorated opium tincture, 0.2 ml.; glycerin, 0.2 ml.

Fig. 4.—Scarring of posterolateral chest.

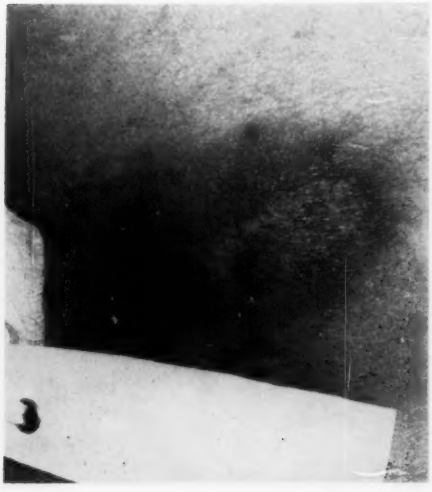

Fig. 5.—Recurrent lesion of posterior neck.

Fig. 6.—Recurrent lesion of the sternal region.

Fig. 7.—Recurrent lesion of the anterolateral chest.

the same appearance as the previous lesion on the posterolateral chest wall except that they were more numerous and more ulcerative (Figs. 5, 6, and 7). At this point, iodide was more strongly suspected, since the only ingredient common to this cough mixture and Quadrinal is potassium iodide. Ammonium chloride cough mixture was discontinued on March 4, and repository corticotropin injection therapy was instituted on March 5. Initially this drug was given in a dose of 60 units daily for a period of 5 days; then the dose was gradually reduced, and it was discontinued 23 days later. Local treatment consisted of saline soaks and Neosporin ointment. The lesions began to regress and were epithelized (healed) in 30 days (Figs. 8, 9, and 10).

Comment

This report concerns a patient who developed an unusual cutaneous manifestation to iodide therapy. Although a single ulcerative chest lesion is a most unusual, if not unique, manifestation of such sensitivity,

Fig. 8.—Scarring of posterior neck.

Fig. 9.—Scarring of the sternal region.

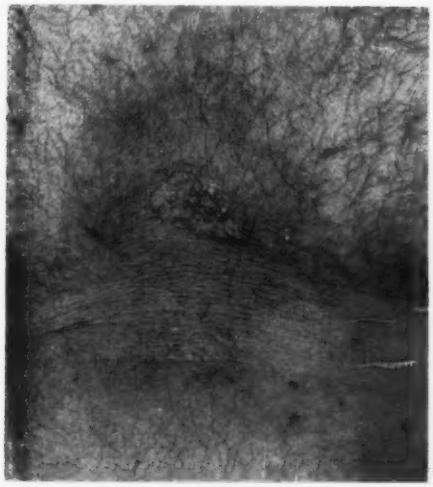

Fig. 10.—Scarring of the anterolateral chest.

the etiologic role of iodide was suspected during the first episode in view of the negative bacteriological cultures, the afebrile course, and the lack of benefit from broad-spectrum antibiotics. The recurrence of the same type of lesion following the reintroduction of iodide confirmed this suspicion, since this was the only change in treatment.

Prior to the development of the intial lesion, the patient had ingested 7.8 gm. of potassium iodide, and preceding the second outbreak he had taken only 1.4 gm. of potassium iodide. On both occasions the medication was administered over a period of six days before the eruption occurred. The second episode, which was severer, resulted from less than one-fifth the amount of potassium iodide responsible for the first episode and probably indicated increasing sensitivity to iodide.

During both episodes of iododerma treatment was exactly the same except for the addition of 740 units of corticotropin in the treatment of the second reaction. These circumstances provided an excellent opportunity for comparing two methods of treatment of identical conditions in the same person. The healing time was measured from the time of discontinuance of iodides and onset of therapy to the time the lesions were completely epithelized. This time measured 31 days without the use of corticotropin and 30 days with its use, which was certainly an insignificant difference. It is of some possible significance to note that the second episode of iododerma was more extensive and severer than the first.

Summary and Conclusions

An unusual ulcerative and carbuncular cutaneous reaction to iodide occurred on two separate occasions in the same person.

The etiologic role of iodide was confirmed, since the original type of lesion was duplicated after the reintroduction of this drug.

These circumstances provided an excellent opportunity for comparing therapy with and without corticotropin.

Corticotropin was used without adverse effect, but in this patient there was no apparent benefit from the use of this hormone.

Arnold F. Straus, M.D., Consultant in Pathology, did the microscopic interpretation of the skin biopsy specimen; Mr. Clarence Gaskins, Chief, Medical Illustration Laboratory, supplied the illustrations.

Veterans' Administration Center.

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Cashew Nut Shell Oil for Hyposensitization Against Rhus Dermatitis

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The requirements for hyposensitizing Rhus-sensitive persons with specific allergens have been given in a previous paper.[1] The present study demonstrates that cashew nut shell oil may be used for this purpose. This material is cheap, easily obtained, stable, and of fairly constant composition.

Cashew Nut Shell Oil

The cashew tree (Anacardium occidentale) is extensively cultivated in Brazil and India because of the edibility of its nut; however, the nut does not give up its prize easily, for the kernel is encased in a tough shell. The natives solve this problem by roasting the nuts at high temperatures until the rind becomes brittle; a sharp blow then delivers the kernel. During the heating, a brownish oil capable of causing severe contact dermatitis is released from the rind. The shell contains about 35% of oil by weight. Heating causes the honeycombed oil-secreting cells to burst open. More efficient recovery is attained by extracting the shells in hot oil from a previous batch. If the oil was originally a stratagem of nature to prevent humans from enjoying the delectations of the nut, modern ingenuity has thwarted the plan. The oil is no longer a repugnant by-product but a valuable raw material for the manufacture of a host of products as diverse as insulating varnishes, floor tiles, brake linings, typewriter rolls, cold-setting cements, etc.[2] When appropriately reacted with aldehydes, resins with remarkably useful and versatile features are formed. The fully "cured" resins are harmless. Millions of pounds of the crude oil are imported annually into the United States. Indeed, it was the dermatitis which American workers experienced that stimulated fundamental chemical enquiries. Though crude, practically all of the oil is phenolic, a property that curiously is, at once, the basis for its industrial use and for Rhus hyposensitization. So it happily turns out that high-grade oils for resin manufacture are also good allergens. The important specifications * of a high-grade oil are that the iodine number (Wijs) must be over 250 (a measure of unsaturation paralleling antigenic activity) and at 350 F treatment with concentrated sulfuric acid causes polymerization to a stiff rubbery mass in less than 19 minutes (a measure of phenolic constituents). Neatly enough, but totally incidental, is the fact that high unsaturation and high phenolic content are measurements of the presence of potent allergens.[3]

Botanical and Immunological Considerations

The cashew tree is one of an immunologically related group of dermatitis-producing plants of the family Anacardiaceae. The others include poison ivy (Rhus radicans) and poison oak (Rhus toxicodendron), the Japanese lac tree (Rhus verniciflua), the mango (Mangifera indica), and the

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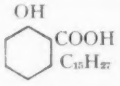
From the Department of Dermatology (Donald M. Pillsbury, M.D., Director), School of Medicine, University of Pennsylvania.

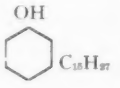
* These specifications are those of the Minnesota Mining & Manufacturing Co., Irvington Chemical Division, Newark 5, N. J. Dr. David Wasserman, of this company, gave generous supplies of a high-grade Brazilian cashew nut shell oil.

Indian ink tree (Semecarpus anacardium). A person sensitized to any one of these will be contact-sensitive to the rest. The reason for this complete cross sensitivity is the common presence of phenols with 15 carbon side-chains. The allergenic constituents of Japanese lac, poison ivy, and the cashew tree have been precisely defined chemically mainly through the extraordinarily effective researches of Dawson and his collaborators at Columbia University.[4] The first two are pentadecylcatechols (dihydric phenols). Cashew oil contains three types of allergens, two phenols, and a resorcinal as follows[5]:

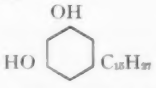
(1) Anacardic acid
(3-pentadecadienylsalicylic acid)



(2) Cardanol
(3-pentadecadienylphenol)



(3) Cardol
(5-pentadecadienylresorcinol)



Actually, each of the above is a mixture of four constituents differing in the degree of unsaturation of the side-chains. Each contains a monoolefin (one unsaturated bond), a diolefin, a triolefin, and a fully saturated chain. Altogether, then, cashew oil contains 12 chemically distinct allergens. The scheme of four constituents differing in side-chain unsaturation is also a characteristic of Rhus antigens.[4]

Obviously, the cashew oil allergens are not heat-labile, considering the high temperatures by which the oil is obtained. However, during the process, anacardic acid is largely converted to cardanol through decarboxylation. About 10% of the oil is cardol; about 70%, cardanol, and the remainder, phenolic polymers formed during heating.[6] Polymerization does not destroy allergenicity. Keil et al.[7] patch-tested Rhus-sensitive persons with the three cashew allergens. They found cardol to be by far the most active allergen, as might have been expected by its having an additional free OH group.

Hydrogenation of cardol saturates the olefinic side-chains and produces a single product, tetrahydrocardol. This resorcinol gives less patch-test reactions than saturated pentadecylcatechol, the corresponding Rhus antigen.[7] Evidently catechols are more potent antigens than resorcinols. One could anticipate that poison ivy oleoresin, with its preponderance of unsaturated catechols, would be more dermatitogenic than cashew oil, in which monohydric phenols are dominant. This was put to the test by simultaneous quantitative patch testing of five Rhus-sensitive subjects with crude cashew nut shell oil, poison ivy oleoresin, and saturated pentadecylcatechol (PDC). The allergens were dissolved in acetone and applied as described previously in the following dilution series: 1:100; 1:1000; 1:10,000; 1:100,000; 1:1,000,000.[1] It is necessary to emphasize once again the great limitations of patch testing for assaying allergenic potency. The method furnishes only a crude estimate. Suffice it to say that poison ivy oleoresin in the above tests not only tended to give reactions at one dilution higher than cashew oil and PDC but these were characteristically more *vesicular*, particularly in the stronger concentrations. The titers of cashew oil and PDC were about the same, but the more vesicular reactions of the latter suggested greater activity. Vesiculation distinguished these three substances more crisply than the titers, which were often vague. Were it not for the 10% of cardol contained in cashew oil, it would doubtless be far inferior even to PDC, the weakest of the poison ivy allergens.

Cashew nut shell oil is a strong primary irritant, much more so than poison ivy oleoresin. Patch tests with undiluted oil produced severe bullous reactions on the forearms of five nonsensitive subjects. Ten

per cent solutions in sesame oil were non-irritating under the same conditions.

Controlled Study of Hyposensitization with Cashew Nut Shell Oil

In undertaking to utilize cashew oil I had no thought that anything really new would be learned about Rhus hyposensitization, in which respect my expectations were fully requited. I shall, accordingly, not repeat what has been given in detail previously.[1]

The pilot study consisted of administering 10% cashew oil orally to 15 Rhus-sensitive adult males.† All of the subjects had previously been hyposensitized with PDC but had returned to their original state of sensitivity. The dosage plan was that utilized previously, under the heading of Conservative Oral Prophylaxis,[1] the details of which are given below. Change in sensitivity was estimated by quantitative patch testing every eight weeks. Within the limitation of the method, cashew nut shell oil proved about equal to PDC in hyposensitizing efficacy. Thirty-five to forty milliliters of the 10% solution (3500-4000 mg.) were needed for maximum hyposensitization.

Subsequently 43 Rhus-sensitive volunteers were given 35 ml. of 10% cashew nut shell oil orally. Their ages ranged from 5 to 62. About two-thirds were males. After treatment, exposure to fresh poison ivy leaves by the finger-leaf test revealed the usual evidences of decreased sensitivity, namely, briefer duration of the dermatitis and often weaker reactions.[1] For all practical purposes cashew nut shell oil may be substituted for PDC. The problems of hyposensitizing with cashew oil are in no wise different than with homologous Rhus allergens. The oil has no special merit for this purpose. Any agent capable of causing a specific allergic dermatitis in Rhus-sensitive persons could be used equally as well, allowing for dose differences. The synthesis of PDC is costly, and it is not now obtainable commercially. Cashew oil is being recommended simply because it is readily available in a useful and fairly consistent form. I shall now give a practical plan of conservative prophylaxis and summarize the present posture of the problem from the clinical viewpoint.

† The subjects were inmates of Philadelphia County Prison, Holmesburg, Pa.

Clinical Considerations

The oil is prepared in the following formulation:

Cashew nut shell oil	10.0
Aerosol OT (American Cyanamid)	2.5
Tenox II (Eastman Kodak)	0.1
Ethyl alcohol	90.0

The oil is first lightly washed with weak sulfuric acid. This precipitates mineral salts and removes amines and other potentially noxious substances. Unwashed oil was not tried. Aerosol OT is a wetting agent; Tenox II is an antioxidant.

The dosage plan is as follows:

First week	1 drop daily
Second week	2 drops daily
Third week	3 drops daily
Fourth week	4 drops daily; thereafter increase by 1 drop every four days to a total of 20 drops daily; continue at this final dose until a total of 35 ml. have been consumed.

The drops are added to a *full* glass of tepid water or other palatable liquid, stirred, and drunk with a glass or disposable straw. In water, the oil forms a milky emulsion; the water should not be ice cold lest the emulsion break. After the first week the daily dose is split into a morning and evening portion; this division of the dose lessens side-reactions. The taste is slightly disagreeable but can probably be disguised. At the final dose the patient will be taking 10 drops morning and night. The liquid should not touch the glabrous skin; yet some intrepid patients drank the emulsion through pursed lips.

Skin eruptions and oral mucous membrane inflammations were the most important and frequent side-reactions. These were never serious. Of the 58 subjects, 5 (9%) developed mild stomatitis and 19 (33%) had to proceed at a slow rate because

of skin rashes. These were patchy or diffuse erythematous, macular, or maculopapular eruptions of the "toxic" or "drug" type, almost always pruritic. Occasionally they were curiously restricted to one area. Pruritus, localized or more general, is a sign of impending rash. It may exist alone if the drops are stopped or the dose is lowered. Pruritus ani occurred only once. This is a frequent and distressing adverse effect with oily vehicles. Administration in the form of an emulsion evidently allows complete absorption of the allergen, hence the low incidence in the present series. Vesicular eruptions were never encountered. Should these appear, the possibility of a bona fide case of Rhus dermatitis from plant contact should be considered. Neither Shelmire [8] with his great experience nor I have witnessed vesicular contact dermatitis-like eruptions, though others declare otherwise.

With this conservative schedule of dropwise ascending doses, severe reactions are headed off in the early stage merely by stopping the medication for a few days. *Actually, the above schedule is merely a guide which is appropriate for the average case of sensitivity; the management of each case is an individual matter.* The dosage scheme is a compromise between the opposing factors of saving time and avoiding distressing side-reactions. Some persons can go much faster, and others get stuck early in the course. There is no way to predict who will be intolerant, for patients will differ greatly in sensitivity and tolerance. The controlling principle is that each person advances toward the final 20 drop daily dose *as permitted by his own tolerance.* Some never get there but must stay at a lower level until 35 ml. have been taken. This, of course, lengthens the time. It is the better part of valor to stop the drops for a few days in the presence of pruritus or a rash; thereafter, progression should be slower, although stoical souls ignore these injunctions. Patients quickly learn how to use their skin as a barometer; many deviate from the schedule according to their adventurousness or hardiness. It has been found that 50 to 100 mg. of cortisone or its equivalent daily will largely (but not always) suppress side-reactions in persons whose intolerance becomes apparent at less than five drops. A suitable practice is to "cover" such persons until they reach 10 drops and then see how they fare with a reduced dosage of 5 drops without corticosteroids.

Depending on tolerance, three to eight months are required for a course. About four months is an average. The treatment should begin not later than February in the northeastern United States. Hyposensitization is temporary; the effects begin to wane in about six weeks, with restitution of the original state of patch-test reactivity in about six to eight months. There is evidence of a lingering effect beyond this time.[1] However, a spring course ending in early summer generally provides suitable protection for the remainder of the season. If exposure is high until fall, a maintenance dose is indicated. Treatment has to be repeated each year, or hyposensitivity may be perennially maintained by five drops of 10% cashew oil daily. Less than this is inadequate. To go through such a lengthy treatment with its potential discomforts, the need must obviously be great. Mildly sensitive persons will not be deeply motivated and do not really need treatment unless attacks are frequent. On the other hand, severe Rhus dermatitis is one of the most maddening of all human afflictions; the victim is seized with a wild, maniacal itching which liquefies the hardiest will and shatters the spirit. While corticosteroids are often of immense help in relieving acute Rhus dermatitis, my experience has been that practically all exquisitely sensitive persons endorse the adage that an ounce of prevention is worth a pound of cure.

Hyposensitization is not desensitization. No highly sensitive person can be rendered completely resistant to poison ivy leaves by conservative oral prophylaxis. The protection is partial and dependent on intensity

of exposure. Therefore, the prophylactic value should not be oversold. Under average circumstances the benefits of hyposensitization are three. In the order of probable attainability these are (1) briefer course (this promise can almost always be fulfilled), (2) less dissemination, and (3) reduced dermatitis. The last two are dependent on exposure and original sensitivity.

Toxicology

Rhus antigens are relatively nontoxic, even when large amounts are given to nonsensitive persons.[1] The important side-reactions are allergic. Their seriousness is a function of dosage. It remains to show that the safety of cashew nut shell oil is comparable to that of Rhus antigens. That this is apparently the case was demonstrated by the following:

1. At the conclusion of conservative oral prophylaxis none of 36 subjects showed significant changes in urinalyses and complete blood cell counts. It is possible that eosinophilia would have been detected in some of these at an earlier stage.

2. The following tests were unaffected when nine nonsensitive subjects received orally 1 ml. of undiluted cashew nut oil daily for one month (this is almost 10 times the recommended dose—urinalysis, complete blood cell count, serum protein and A/G ratio, blood urea nitrogen, serum bilirubin, sulfabromophthalein (Bromsulphalein) excretion, thymol turbidity, and phenolsulfonpthalein excretion.

3. Six nonsensitive persons were given the following series of 10% cashew oil in sesame oil intramuscularly at weekly intervals—0.5 ml., 0.5 ml., 1.0 ml., 1.0 ml., 1.0 ml., 1.5 ml., 1.5 ml., 2.0 ml., 2.0 ml. Local tenderness developed in all after 1.5 ml. Aside from modest degrees of eosinophilia in three of the six, the blood cell counts and urinalyses remained unchanged.

Summary

Hyposensitization of Rhus-sensitive persons may be satisfactorily achieved by the graduated oral administration of 10% cashew nut shell oil in ethyl alcohol. The results are comparable to those with pentadecylcatechol, one of the homologous Rhus antigens.

Skin rashes and stomatitis are the only important side-reactions. These are fairly frequent but are neither hazardous nor too discomforting when proper care is exerted.

Duhring Laboratories, University of Pennsylvania (4).

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A Study of Certain Contributory Factors in the Development of Vitiligo in South Indian Patients

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Introduction

Vitiligo is a disorder of pigmentation which has baffled the medical world for centuries. It should be differentiated from the more inclusive descriptive term leukoderma, which may also include depigmentations due to obvious local causes, such as burns or wounds, chronic eczematous conditions, psoriasis, leprosy, or syphilitic leukomelanoderma. Although there is no restriction of physical endurance, work capacity, or life expectancy, vitiligo patients frequently suffer from severe psychological trauma because of the disfiguration of unsightly white patches, especially if these occur on exposed areas of the face or extremities.

From my observations on 410 cases of vitiligo seen over a period of three years in the Dermatology Clinic, Christian Medical College Hospital, Vellore, South India, I have been impressed by the variability in distribution of lesions, type of lesions, course of the disease, and particularly in response to treatment. Although the psoralen derivatives now offer hope for cure to a large percentage of vitiligo patients, dermatologists still cannot explain why these drugs are remarkably effective in some cases yet apparently useless in others.

When we consider the multiplicity of factors governing melanogenesis—dietary, physical, hormonal, biochemical, hereditary—we may assume that different etiological factors may be operative in different cases. Some of these, but not all, may respond to treatment with the psoralen drugs.

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"Normal" skin color may be considered a balance between factors leading to pigmentation, on the one hand, and depigmentation, on the other. A lack of one factor or excess of another may disturb the equilibrium in favor of either hyperpigmentation or depigmentation. Furthermore, depigmentation may be due either to the failure of formation of melanin or to the destruction of melanin normally produced. Clinical vitiligo is probably not a single disease process but rather the end-result of several factors operating concomitantly to produce depigmentation. It is my purpose in this paper to discuss certain factors which may be contributory to the development of vitiligo in my patients in South India.

Statistics Regarding Incidence

Over a period of three years, 410 cases were seen in the Dermatology Clinic. With an average of 3500 new dermatology cases per year, this would mean an incidence of about 4% of the clinic patients. The incidence of vitiligo in the general population in South India is not known.

Age and Sex

Of these patients, 210 (52%) were men, 118 (29%) were women, 28 (7%) were boys under 12 years of age, and 49 (12%) were girls under 12. In five cases the age was not recorded. It may be significant that there were almost twice as many men as women and twice as many girls as boys. Age on admission varied from 6 months to 70 years, but the average for males was 29 years and for females, 21 years. Similarly the age of onset of vitiligo varied from soon after birth to 69 years, with the aver-

TABLE 1.—*Age Incidence of Onset of Vitiligo by Decades*

	Age, Yr.														Total, No.
	0-9		10-19		20-29		30-39		40-49		50-59		Over 60		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Male	18	9	58	29	61	31	37	18	11	5.5	12	6	3	1.5	200
Female	48	34	46	32	15	10	16	11	14	10	4	3	--	--	143

age for males at 26 years and for females at 18 years. Duration of the disease at time of admission varied from 2 weeks to 30 years, with an average of 3 years for both males and females.

Hormonal Factors

Because of a clinical impression that we were seeing more cases of vitiligo among young girls than boys, we studied the onset of the disease by decades in both males and females in 343 of our cases. The results, as seen in Table 1, were very interesting. Most women start depigmentation before the age of 20, whereas men are most likely to start depigmentation between the ages of 10 and 40 years. This finding, coupled with the sex incidence indicated above, leads one to surmise that the higher level of ovarian hormones in women over 20 may provide a protective influence against depigmentation. The hyperpigmentation of the areola and chloasma seen during pregnancy is well known. Furthermore, progesterone has been shown to increase the activity of melanogenocytes in vitro.[1] The only decade after 20 years in which women had a higher incidence of the onset of vitiligo than men in my cases is between 40 and 50 years, when there is a decrease in ovarian stimulation due to menopausal changes.

Three women in the series dated the onset of vitiligo from the termination of childbirth, and one indicated that it followed abortion. Two others had a diagnostic dilatation and curettage during the course of the disease; one was diagnosed as having cystoglandular hypoplasia, and the other, a case of primary sterility, pathology not reported. Although the information on these cases is incomplete, the possibility may be considered that a sudden drop in circulating progesterone or estrogens may be a precipitating factor in vitiligo.

Nutritional Factors

The role of nutritional deficiencies in pigmentary disturbances is difficult to determine accurately, because most patients with a poor diet have multiple deficiencies. There is some evidence to show that vitamin B complex factors, notably pantothenic acid and perhaps biotin, are essential to pigmentation.[2] The hyperpigmentation of pellagra is probably secondary to the local dermatitis and consequent decrease in sulfhydryl compounds in the skin.[3] The same mechanism would seem to apply to the hyperpigmentation at sites of hair follicles in the follicular hyperkeratosis of vitamin A deficiency.[4] On the other hand, Sulzberger and Lazar have described a chloasma-like hyperpigmentation in patients receiving high doses of vitamin A which disappeared when the medication was stopped.[5] Ascorbic acid inhibits pigmentation in vitro probably because of its reducing properties.[6]

Diet habits were studied in 178 of the cases. Of these, 47 (26%) had a vegetarian diet, and 131 (74%) had a nonvegetarian diet. However, a large number of the latter group were able to afford meat or eggs only once or twice a month and should properly be considered as vegetarians. The average diet in this area is probably deficient in protein and vitamins A and B. It consists primarily of rice and vegetables with a less amount of other grains, milk, and fruit. Limes and tamarind are plentiful and cheap during certain seasons of the year and are used both cooked and uncooked in chutneys

and sauces. It is a popular custom among all adults to chew a mixture of a green betel leaf reputedly rich in ascorbic acid, araça nuts, and a calcium paste called *chunam*.

Nutritional status was further studied in 151 of these cases. Eighty-two patients (54%) were classified as good, with no clinical evidence of malnutrition. Fifty-eight (39%) classified as fair either had mild symptoms of vitamin deficiency or were underweight. Eleven patients (7%) classified as poor were either grossly malnourished or showed severe symptoms of vitamin deficiency. Theoretically hypoproteinemia could result in an insufficient supply of tyrosine for the formation of melanin. Only one of my cases (0.7%) had edema and ascites probably due to a protein-deficient diet. However, he also had multiple vitamin deficiencies.

Hemoglobin was checked in 196 cases. Of these, 129 (66%) had a hemoglobin level of over 12.0 gm/100 ml., which in this area is considered good. Fifty-one (26%) had a hemoglobin level between 10 and 12 gm/100 ml.; twelve (6%), between 8 and 10 gm., and four (2%) between 4 and 8 gm. Blood films of 11 of those with levels below 8 gm. showed hypochromia. Red cells of four of these were microcytic; the remainder were normocytic. All were advised treatment with ferrous sulfate. Five who returned for repeat hemoglobin studies showed improvement with therapy, three of them to normal values. Robert et al. reported hyposideremia in vitiligo and decreased iron content of depigmented skin.[7] Further study of this aspect is needed. Allison and Curtis reported an unusually high incidence of pernicious anemia in their vitiligo patients, but I did not have a single case in my series.[8] It may be that the coincident nutritional deficiency was responsible for this finding rather than the anemia. It should also be noted that pernicious anemia is very rare in Indian patients.

If any of these deficiencies are significant factors in causing vitiligo in my patients, theoretically they should be present in a higher percentage than in the normal population. Table 2 shows a comparison of clinical findings between my vitiligo patients and the population of Pennathur, a village five miles from Vellore, in which there was only one case of vitiligo. These groups are not exactly comparable, because a fair proportion of my patients are from the city and have different food habits. Nevertheless, it is interesting to note that in general my group of vitiligo patients appeared to be better nourished than this group of villagers.

A significant observation has been made by Dr. William Todd, Mission Hospital, Jalna, Deccan, India.[9] In this hospital, in which 112,000 outpatients are treated every year, he would normally see 150 to 200 patients with vitiligo, or an average of 3 or

TABLE 2.—*Comparison of Clinical Findings of Nutritional Deficiencies* and Hemoglobin Study† in Vitiligo Patients and Pennathur Rural Health Survey*

	Vitiligo Patients		Pennathur Survey	
	No.	%	No.	%
Clinical Findings				
Vitamin A deficiency				
Eyes, conjunctiva				
Xerosis	12	8	116	17
Bitot's spots	7	5	32	4.7
Skin				
Dry and rough ‡	15	10	100	14.6
Phrynoderma	4	3	29	4.3
Vitamin B deficiency				
Angular stomatitis	11	7	92	13.5
Buccal stomatitis ‡	8	5	19	2.8
Glossitis	2	1	23	3.4
Burning of mouth ‡	2	1	--	----
Neuritis, numbness, paresthesias of extremities ‡	3	2	--	----
Ascorbic acid deficiency				
Bleeding gums ‡	1	0.6	63	9.3
Protein deficiency				
Pitting edema ‡	1	0.6	16	2.3
Hemoglobin study				
0—3.9 gm/100 ml.	--	--	1	0.2
4—7.9 gm/100 ml.	4	2	32	5.4
8—9.9 gm/100 ml.	12	6	68	11.4
10—11.9 gm/100 ml.	51	26	282	47.3
Over 12.0 gm/100 ml.	129	66	213	35.7

* One hundred fifty-one vitiligo patients examined; six hundred eighty-one Pennathur survey patients examined.

† One hundred ninety-six vitiligo patients examined; five hundred ninety-six Pennathur patients examined.

‡ Signs which may also be explained by other diseases.

4 new cases every week. After one year of famine in this area when large numbers of people were treated for multiple deficiencies, particularly scurvy, avitaminosis B, and hypoproteinemia, he saw only one patient with vitiligo during an entire year! One factor that differentiates his group of patients from my large number of vitiligo patients, is the high incidence of scurvy in his group as contrasted with its singular absence in my group. As mentioned above, ascorbic acid inhibits pigment formation in vitro. It may be that under certain conditions a low intake of ascorbic acid may be a protective factor against the clinical development of vitiligo.

Hereditary Factors

For many years investigators have considered the influence of hereditary factors in vitiligo. Sidi and Bourgeois-Gavardin reported a family incidence of 16%.[10] Behl, in Delhi, reported an incidence of 18% in one series and 12% in another.[11] Of 244 patients questioned in my series, 29 (11%) gave a family history of vitiligo. However, because of the associated stigma, I would suspect that the actual incidence is higher.

Toxic Factors

In certain cases the spread of vitiligo is so rapid, involving large areas of the body within a few days or weeks, that it would appear to be due to a destruction of melanin pigment rather than merely a failure of melanin formation. This type may follow a severe illness or drug therapy and implies the production of melanodestructive toxins in the body. Ormsby and Montgomery reported a case of vitiligo and canities following typhoid.[12] One of my patients reported the onset of vitiligo immediately after an attack of typhoid; nine others gave a history of typhoid a year or more prior to the onset of vitiligo. Three of my patients dated the onset from an attack of malaria; five others had had malaria some time prior to the vitiligo. Many had had nonspecific fevers for which a diagnosis was not made just prior to the development of vitiligo.

Inhibition of pigmentation in vitro has been experimentally produced by various substances, i. e. sulfhydryl compounds, such as dimercaprol (BAL) or glutathione [13,14]; competitive inhibitors, such as tyrosine derivatives; substances that combine with O-dihydroxy groups, such as sodium molybdate [2]; substances that combine with orthoquinones, such as aniline,[6] and hydroquinones.[15]

None of my patients were receiving thiourea or thiouracil. One patient was given three courses of diethylamine acetarsone (Acetylarsan) for eosinophilia. During the third course of injections, almost two years after the first, depigmented macules appeared and rapidly spread throughout the body. As arsenic typically produces hyperpigmentation, it is difficult to understand how it could be responsible for the depigmentation in this case, unless the depigmentation was a type of allergic or sensitization reaction.

Fig. 1.—Hyperpigmentation of cheeks before treatment.

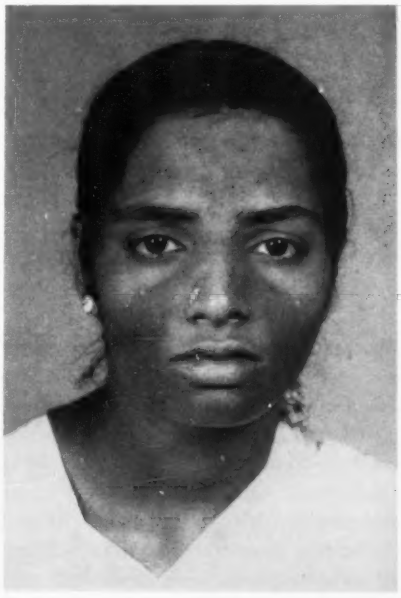

Fig. 2.—Depigmentation of cheeks following local application of monobenzone twice daily for three weeks.

One patient, not included in this series, was given an ointment containing 20% monobenzone (Benoquin, Paul B. Elder Co.) for hyperpigmentation of both cheeks. This area rapidly depigmented after application for only two weeks (Figs. 1 and 2). Hydroquinone has been shown to be a specific tyrosinase poison.[15] However, as other cases of hyperpigmentation responded to this treatment only after four to six months, if at all, it would seem that certain persons are more sensitive to the action of this compound than others.

Allergic Factors

It was a frequent observation in our clinic that a transient hypopigmentation, particularly of the chest and back, was associated with intestinal parasites. Sometimes these hypopigmented macules were slightly erythematous. Other cases of urticaria and maculopapular dermatitis without change in pigmentation were traced to intestinal parasites and disappeared with appropriate treatment. In our routine laboratory tests we found such a high incidence of helminthiasis with eosinophilia that we decided to investigate further the possibility of an allergic mechanism operating in cases of vitiligo. Certain parasites, notably Ancylostoma, Ascaris, and Acarus scabiei, all very prevalent in this area, are well known for their allergenic properties.

Stool examinations were performed in 206 of our patients. Of these, 110 (53%) were negative. Unfortunately, only 15 of these cases came for repeat examinations and were still negative. Ninety-six (47%) were positive for intestinal parasites. Nineteen (9%) had multiple infections. The results are tabulated in Table 3, again in comparison with the village group in Pennathur.

Two hundred fifty-three patients were studied for the possibility of allergic or other skin conditions. Of these, 27 (10.7%) had scabies, 2 (0.8%) had contact dermatitis, and 24 (10%) complained of itching without clinical involvement.

White blood cell count and differential count were determined for 216 patients. One hundred nineteen (55%) had eosinophilia of more than 7% eosinophils, with a normal total count. In these cases, 57 (26%) were positive for intestinal parasites, 52 (24%) were negative, and in 10 (5%) the stool was not examined. Of the patients without eosinophilia, 27 (13%) were positive for intestinal parasites, and in 12

TABLE 3.—*Comparison of Incidence of Intestinal Helminths in Vitiligo Patients and Pennathur Rural Health Survey*

	Vitiligo Patients *		Pennathur Survey †	
Intestinal Helminths	No.	%	No.	%
Normal	110	53	87	19.4
Escherichia coli			234	52.2
Hookworm	61	30	200	44.6
Giardiasis	11	5	39	8.7
Whipworm	13	6	10	2.2
Roundworm	16	8	3	0.7
Endameba Histolytica	3	1.5	2	0.4
Others	23	11.5	151	33.7

* Two hundred six patients examined.
Four hundred forty-eight patients examined.

more cases (6%) with parasites differential count was not reported. Of the 27 cases of scabies, 5 showed eosinophilia with a negative stool report; 7 cases with eosinophilia also had worms, and in 7 cases the differential count was normal. In the remaining eight cases, the differential count was not reported.

Banerjee in his series of 125 cases in Calcutta reports an incidence of 85% Endameba histolytica and suggests that liver damage may be an important etiological factor.[16] There were only three cases of amebiasis (1.5%) in my series. One hundred ninety-five patients were questioned regarding a history of prior jaundice or liver trouble. Only 20 (10%) gave a history of jaundice, and 2 (1%), of liver and gallbladder disease. In all of these cases liver-function tests were normal. Van den Bergh reaction and thymol turbidity tests performed on an additional 76 cases without history of liver trouble or jaundice were also normal.

These findings show that although in my study there was a high incidence of intestinal parasites, this corresponded roughly with the nonvitiligo population of Pennathur. Incidence of whipworm and roundworm was slightly higher in my series. There was no evidence of liver damage. Over half of my patients did have eosinophilia of more than 7% eosinophils, indicating an allergic response on the part of the body. In half of these helminthiasis or scabies may have been responsible for eosinophilia.

Psychogenic Factors

Psychic trauma and nervous tension are frequently mentioned as etiologic factors in vitiligo. There are many authentic cases on record of hair turning gray within a few days after an emotional shock. Similarly, premature graying of hair commonly follows an extensive period of nervous strain or exhaustion.

The significance of the origin of the pigment-forming melanogenocyte in the basal layer of the dermis has been much debated in the literature. Although Bloch, in his original study on pigment formation, considered these to be modified basal cells, recent investigators have shown that they are probably of neural origin. This raises the question of the possibility of central nervous system control or influence on pigmentation. There appears to be a relationship between the encephalitis and neural manifestations of the Vogt-Koyanogi syndrome and the subsequent vitiligo of the forehead and eyebrows. One patient with this syndrome was admitted for treatment of uveitis but was discharged before further dermatological investigations could be conducted.

It has been shown that epinephrine (Adrenalin) and arterenol (Noradrenalin) have a local inhibitory effect on melanogenocytes in vitro.[1] In certain cases continuous excessive production of epinephrine through stimulation of the sympathetic nervous system might conceivably be responsible for inhibition of pigment formation. I did not undertake a study of possible psychogenic or tension-producing factors in my patients.

TABLE 4.—*Distribution of Depigmented Lesions in Vitiligo*

Site of Lesion	No.	%
Head		
Face	134	13
Lips	110	11
Scalp	34	3
Neck	30	3
Total	308	30
Trunk		
Chest	77	7
Back	68	7
Body	28	3
Waist	25	2
Genitalia	28	3
Total	226	22
Extremities		
Arms	94	9
Legs	162	16
Hands	118	12
Feet	112	11
Total	486	48

Distribution of Lesions

In all 410 cases the distributions of depigmented lesions in different parts of the body were recorded (Table 4). One hundred eighteen cases (30%) had single lesions. The remaining 292 patients averaged lesions in three different locations. The commonest locations were the face and the extremities. It is interesting to note that the number of lesions on the legs is almost twice that on the arms, although the lesions on hands and feet are almost equal in number. It has been suggested that the reason lentigines and pigmented nevi are commoner on the upper extremities than on the lower is that melanocyte-stimulating hormone released from the pituitary is quickly destroyed in the blood stream and, hence, more is available to the upper extremities. Perhaps this same factor is operating here in reverse to prevent depigmentation more readily in the upper extremities.

It was my clinical impression that lesions of the hands and feet frequently involved the tips of the fingers and toes around the nail beds. Similarly, a large percentage of face lesions were limited to the lips only. Although lesions of the cheeks or chin and the dorsa of hands or feet responded well to treatment with psoralen drugs, depigmentation at the extreme periphery, i. e., lips, fingers, and toes, responded very poorly to psoralen treatment. The reason for this is not known.

Conclusion and Summary

Vitiligo is a disorder of pigmentation of the skin which may be caused by a number of factors operating either singly or in combination. Possible contributory factors in the development of vitiligo in 410 patients seen in the Dermatology Clinic, Christian Medical College Hospital, Vellore, India, are discussed. These include hormonal factors, hereditary influence, and nutritional deficiences, primarily deficiency of vitamin B complex. The role of vitamin A is uncertain. It is also possible that when depigmenting factors are operative in the body a low ascorbic acid level may prevent clinical depigmentation. Toxic factors, an allergic diathesis possibly in conjunction with intestinal parasites, and psychogenic factors may have a contributory role in some cases.

Vitiligo is commoner in men than in women but also commoner in girls under 12 years of age than in boys. In women the onset of vitiligo is usually before the age of 20; in men it is likeliest to appear between the ages of 10 and 40. This may indicate that female hormones have a protective influence against the clinical development of depigmentation. Lesions of vitiligo are shown to occur most frequently on the face and the extremities. In my patients the number of lesions on the legs was almost twice that on the arms, although the numbers of lesions on the hands and on the feet were almost equal.

The Department of Public Health, Christian Medical College Hospital, gave permission for use of certain statistics from the Pennathur Rural Health Survey.

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The Relationship of Pruritus and Local Skin Conditions to the Development of Vitiligo

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It is a common observation that various types of local trauma to the skin, such as burns, x-rays, inflammatory skin diseases, or pruritic conditions, initially cause a hyperpigmentation but if severe or of long duration may cause depigmentation. Usually, when the irritating factor is removed, the skin again repigments.

A large number of the vitiligo patients seen in the Dermatology Clinic of the Christian Medical College Hospital, Vellore, South India, gave a history of some type of skin involvement or irritation in the specific area which later depigmented. In these cases depigmented macules also appeared in other nonaffected parts of the body. Ormsby and Montgomery [1] state that vitiligo "occurs in association with or follows certain cutaneous diseases such as lichen planus, psoriasis, alopecia areata and local pruritis. . . . It occasionally follows local irritation, trauma through scratching and irritant applications such as formalin." G. Asboe-Hansen [2] reports an incidence of pruritic skin diseases in 50 of his series of 75 patients. Pardo-Costello [3] has described a condition known as achromia parasitica in association with certain fungus infections of the skin, notably tinea versicolor.

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Fig. 1.—Depigmentation following angular stomatitis and buccal stomatitis.

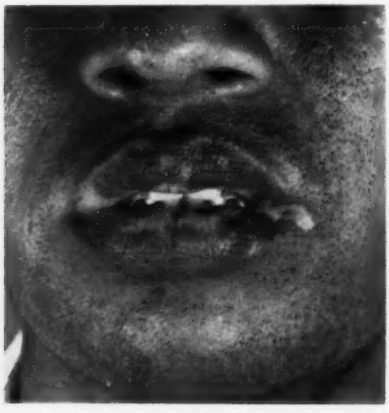

Fig. 2.—Vitiligo of waist of two years' duration in an area of pressure from tightly worn sari.

I studied this aspect in 253 of my vitiligo patients. One hundred twelve (44%) gave a history of prior skin disease in an area of depigmentation, twenty-four (10%) complained of itching without clinical involvement, and thirty-nine (15%) had depigmentation in areas of constant pressure or irritation, such as the waist, where the Indian sari is tied very tightly; the lips, in heavy

Fig. 3.—Vitiligo of hand and webs of fingers in patient with scabies.

smokers, or the forehead, in a person who habitually wears a hat (Figs. 1 and 2). Seventy-eight patients (31%) gave no history of skin disease, scabies, or itching prior to the development of vitiligo.

Associated skin diseases included scabies (27); chronic eczema (12); tinea (10); impetigo or boils (9); local injury (12); depigmentation of lips following fever, with dry, cracked lips (9); ulceration of lips or mouth (6); seborrheic dermatitis (3); caustic native treatment (3); chickenpox (3); ulceration of genitalia (3); excoriations (3); angular stomatitis (2); smallpox (2); pediculosis capitis (2); pediculosis pubis (1); contact dermatitis (2); lupus erythematosus (2); trichomonal vaginitis, with depigmentation of labia (2), and one case each of alopecia areata, psoriasis, vaccinia, sycosis barbae, scleroderma, and dermatitis of unknown etiology. A few had more than one skin disease, with depigmentation in both areas of involvement. Scabies is included in this category in only those cases in which sites of predilection such as the webs of the fingers, the waist, or the buttocks were depigmented (Figs. 3 and 4).

Histological Studies

In order to study the relationship between depigmentations and skin diseases, biopsies were performed in 44 cases with pigmentary involvement as follows: depigmentations—vitiligo (20), chronic eczema (2), lupus erythematosus (2), undiagnosed nonspecific dermatitis (3), syphilis (2), psoriasis (1), canities (1), chemical burn (1); hypopigmentations; tuberculoid leprosy (6); hyperpigmentations—nevus unius lateris (2), erythema multiforme (1), hyperpigmentation following injections (probably arsenic) (1), nonspecific dermatitis (1), and pigmentation following accidental application of a solution of a preparation containing ammoidin and ammidin (Meladinine) on normal skin (1).

In general, the amounts of pigment seen in the basal layer on both dopa and hemotoxylin and eosin stains corresponded with the degree and location of pigmentation seen clinically, i. e., heavy pigment deposition in normal brown skin, patchy deposition in tan or hypopigmented skin, and no pigment in depigmented skin or untreated white patches of vitiligo. All biopsies included

Fig. 4.—Depigmentation of scabietic lesions of arms and chest.

section through adjacent pigmented or normal skin.

In one case of lupus erythematosus the area of central depigmentation on the cheeks rapidly became hyperpigmented after three weeks of quinacrine (mepacrine) therapy. Findings on a second biopsy showed that this was due to large numbers of pigment-filled chromophores in the dermis, though the basal layer was still devoid of pigment. This indicates that clinical hyperpigmentation is not necessarily a sign of stimulated melanogenesis in the basal layer of the epidermis and confirms the value of biopsies in making an accurate diagnosis of the degree and nature of hyperpigmentation.

The extent of inflammatory infiltrate seen in cases of vitiligo was greater in those cases which clinically showed erythema due to exposure to sunlight or local application of Meladinine solution, which is known to be a photosensitizing agent. In all other depigmentations inflammation was predominantly perivascular or perifollicular and greater in the depigmented area than in the adjacent pigmented area. In the case of canities, a patchy alopecia in the beard area had preceded the growth of gray hair. Histologically, pigment was present throughout the basal layer except in the hair follicles and one tiny area adjacent to a hair follicle. There was also perivascular infiltrate and extensive follicular plugging.

Pathology in the cases of hyperpigmentation was varied and could not be correlated with the location or the degree of hyperpigmentation. Three cases showed a densely pigmented basal layer but minimal or no inflammatory infiltrate in the dermis.

Eighteen cases of syphilis with depigmentation were studied. Of these, 14 had involvement of the hands or feet, especially the palms and soles in a typical melanoleukoderma. In the other four cases the scalp, arms, face, and genitalia, areas which may also have been the site of secondary syphiloderm or primary chancre, were depigmented.

The patient may not give a history of clinical maculopapular eruption or scaling before depigmentation. However, there may be intradermal inflammation as a result of spirochetal invasion of the dermis. Findings on biopsies of the border of depigmented lesions in two syphilitic patients showed considerable dermal inflammatory infiltrate, which was heavier in the depigmented area than in the adjoining pigmented area. Clinically the skin in these cases was of normal texture without evidence of inflammation.

A similar finding may also explain the difference in degree of hypopigmentation in two basic categories of lesions in leprosy. Clinically lesions of tuberculoid leprosy are hypopigmented with clearly demarcated margins. Because of involvement of the sympathetic nerves, they are dry and show a loss of sweating in the exact area of hypopigmentation. As the disease progresses, there is also loss of temperature sensation, touch sensation, and sensation on pin prick. In biopsy sections, there is a perineural and perivascular infiltrate in the subpapillary layer of the dermis which corresponds to the area of pigment loss. Lepromatous lesions, on the other hand, are slightly erythematous and exhibit a peculiar shine demonstrable in an oblique light. The degree of hypopigmentation is much less, and the margins are indefinite, and so they are not as conspicuous as tuberculoid lesions. Histologically round-cell infiltration is diffusely distributed in the deeper layers of the dermis, leaving a conspicuous clear zone between the epidermis and the granulomatous infiltration. Because nerves are involved much later in this form of leprosy, there is little or no involvement of nerves in the corium and no loss of sweating in early stages.[4]

Biopsy specimens of six patients with tuberculoid leprosy were studied, three of them with dopa and alkaline and acid phosphatase stains to note changes in pigment deposition and nerve involvement, respectively. All cases showed a greater degree of inflammatory infiltrate in the hypopigmented

area than in the adjacent normally pigmented skin. Frequently pigment was present in the basal-cell layer in a patchy distribution, accounting for the clinical hypopigmentation of the lesion.

These studies indicate that in inflammatory skin conditions depigmentation is most likely to take place in the area of greatest inflammatory infiltrate. This is frequently seen clinically in chronic eczema in which depigmentation takes place in the center of a hyperpigmented lichenified lesion. In vitiligo, however, an inflammatory infiltrate is associated with the depigmentation only when there is a superimposed clinical erythema or inflammatory response due to ultraviolet irradiation or local application of a photosensitizing drug.

When the inflammatory infiltrate is in close proximity to the basal layer of the dermis, we may assume that temporary destruction or inhibition of melanogenocytes may take place by mechanical pressure or chemical factors produced by local injury.

When the inflammatory infiltrate is primarily perifollicular, perivascular, or perineural, the possibility of an alternative mechanism may be raised. It has been shown that dopa is a precursor of arterenol (norepinephrine) and epinephrine (Adrenalin) as well as of melanin. Von Euler [5] demonstrated that arterenol was carried by sympathetic nerves running to the spleen. It may be that dopa could be carried along sympathetic nerves in the same manner to the skin. If this is so, section or destruction of these sympathetic nerves should result in loss of pigment.

Confirmation for this hypothesis may be found in a comparison of pathology of the tuberculoid and lepromatous leprosy lesions mentioned above. In tuberculoid lesions, in which sympathetic nerves are involved, there is a greater loss of pigment in the basal layer than in lepromatous lesions, which show nerve involvement comparatively late in the disease.

It may be that in the localized depigmentation of chronic inflammation perineural inflammation results in a decrease in the amount of dopa which may reach the skin along the sympathetic nerves. This accounts for the reversibility when the inflammatory process is cleared up. In vitiligo cases this factor of local irritation is probably a secondary or contributory factor. When depigmenting forces are operating in the body, sites of previous inflammation, irritation, or pressure are depigmented early in the disease.

If this mechanism is responsible for certain types of depigmentation, loss of sweating should accompany loss of pigment, as in tuberculoid leprosy lesions. Although I have not studied the sweating mechanism in any of my vitiligo cases, clinically a large proportion of these lesions are dry to touch, whereas surrounding pigmented skin is soft and of normal texture. In these cases the patient may complain of itching both before and after treatment with psoralen drugs. I found that this itching is relieved by simple lubrication of the skin with hydrous wool fat (lanolin) or oil. Ormsby and Montgomery state that anhidrosis occurs "in those conditions in which destructive changes have taken place in the skin. It is common to many dermatoses, as, for example, psoriasis, erysipelas, and some forms of eczema; but in these the symptomatic character of the anomaly is shown by the fact that when the skin is relieved of these cutaneous troubles the function of sweat secretion is restored." [6]

In vitiligo, of course, there is no loss of sensation, but there were frequent complaints of itching associated with dry skin. Itching may also be a sign of irritation of the superficial sensory nerves. In chronic skin inflammations also there is a slight loss of superficial touch sensation.

Treatment of Vitiligo

Eighty-two patients in this group investigated for prior skin trouble, itching, or pressure factors received treatment with psoralen drugs. Their response was classified according to the percentage of repigmentation in a lesion as follows: excellent, 95% to

Response to Treatment of Patients With and Without Irritation

	Response							
	Excellent		Moderate		Poor		Total	
	No.	%	No.	%	No.	%	No.	%
Irritation present	34	54	14	22	15	24	63	100
Irritation absent	13	68	2	11	4	21	19	100

100% repigmentation; moderate, 25% to 94% repigmentation; poor, 0% to 24% repigmentation. As most of the patients had treatment for less than the minimum of six months suggested, those in the moderate group are expected to repigment further with continued treatment.

Sixty-three patients (77%) gave some history of irritation or prior skin disease in a depigmented lesion of vitiligo. Nineteen (23%) gave a negative history. As we can see from the Table, the response in these two groups of patients to psoralen treatment is similar. However, the group with prior irritative factors may act a little more slowly to treatment than those without irritation, as shown by the large percentage of the former in the moderate classification. But the percentage of those with a poor response, who may not be capable of responding to psoralen treatment, is the same in the two groups.

Summary and Conclusion

A study of prior skin disease, itching, and irritation in 253 patients with vitiligo seen in the Dermatology Clinic, Christian Medical College Hospital, Vellore, South India, is presented. Of these, 44% gave a history of prior skin disease in an area of depigmentation, 10% complained of itching without clinical involvement, and 15% had depigmentation in areas of constant pressure or irritation.

Findings on biopsies of chronic skin conditions with depigmentation show a greater amount of inflammatory infiltrate in the depigmented portion of the section than in the adjacent pigmented skin.

Findings of vitiligo do not necessarily include an inflammatory process unless there has been superimposed erythema due to ultraviolet irradiation or local treatment.

In inflammatory skin conditions inhibition of melanogenesis may be due to mechanical pressure or chemical factors produced by local injury.

Arterenol (norepinephrine) is carried by sympathetic nerves running to the spleen. If its precursor, dopa, may likewise be carried by sympathetic nerves to the skin, perineural and perivascular inflammation might result in a decrease in the amount of dopa which reaches the epidermis. Confirmation of this hypothesis is suggested by a comparison of clinical and pathological findings in tuberculoid and lepromatous leprosy.

Inflammation and prior irritation are not primary etiological factors in the development of vitiligo. However, when depigmenting factors are operative, prior irritation may determine the site of depigmentation in vitiligo.

Response to treatment with psoralen drugs may be a little slower in vitiligo patients with a history of prior skin disease or irritation than in those patients without irritative factors.

Dr. Gordon Hadley, formerly Head of the Department of Pathology, Christian Medical College Hospital, gave assistance in reading histological sections. Dr. Hadley is now at College of Medical Evangelists, Loma Linda, Calif.

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Unusual Micrococcal Cutaneous Reactions

Review of Some Basic Tenets of Micrococcal Bacteriology and Drug Resistance and Presentation of Two Cases

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The problem of antibiotic-resistant micrococci * is ubiquitous in contemporary medicine. As newer antibiotics are developed they not uncommonly control the organisms initially; however, within a short period micrococci develop resistance to the newer products. Another approach to this problem has been the use of combinations of antibacterial agents to delay the emergence of micrococcal resistance. However, Dowling and co-authors decry the general use of combined therapy for the following reasons: 1. Inadequate therapy may be encouraged by the use of fixed combinations. 2. An increase in hypersensitivity and toxicity may occur with the use of two drugs instead of one, and, in the event of a reaction, it may be impossible to tell which drug was responsible. 3. Bacterial resistance to either or both of the drugs is probable. 4. An accumulation of antibiotic-resistant bacteria will probably occur within hospitals or other semiclosed communities. 5. If the present trend of antibiotic combinations continues, rational chemotherapy will become chaotic.

This entire problem is extremely difficult and may well be resolved by further basic research into the enzyme systems and total ecology of the offending organisms.

In recent months on the dermatologic service of the University of Minnesota Hospitals, I have studied two unusual micrococcal cutaneous reactions. The patient in the first case was a nurse who had a severe ulceroglandular syndrome associated with latent diabetes. The second case involved a housewife who presented a generalized pustular eruption associated with latent diabetes and a pancreatic carcinoma. It is likely that unusual micrococcal clinical patterns will be seen not infrequently in relation to antibiotic-resistant micrococci, either as a primary disease or as a secondary infection complicating debility, diabetes, carcinomatosis, alcoholism, nutritional disturbances, hypogammaglobulinemia or agammaglobulinemia (primary or secondary types), long-term steroid therapy, and the lymphoma-leukemia group (with or without cytotoxic therapy).

Pillsbury and Kligman have set forth criteria for the diagnosis of such secondary bacterial infections, namely, a preceding local or systemic disturbance which facilitates the advance of various bacteria within the skin. Brown and Kligman reported two cases and cited four more of pyodermas which resembled North American blastomycosis and other mycotic granulomas. In all but one of the cases a predisposing condition, especially alcoholism and nutritional deficiency, was present. The cause was considered to be a superimposed bacterial infection, micrococci predominating. Both reported patients responded rapidly to antibiotic and supportive therapy.

Basic Bacteriologic Tenets

Enzyme systems, as concern bacteria, may be divided into constitutive systems, which are formed even in the absence of specific substrate, and adaptive systems (induced

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* Micrococcus in this paper will refer to Micrococcus pyogenes var. aureus (coagulase-positive).

enzymes), which generally require the presence of specific substrate (inducer). In the latter instance, if the substrate is withdrawn the adaptive enzyme systems may be diluted and lost (deadapted). Adaptive systems require a lag period for production of enzymes. New characteristics resulting from genetic mutation are expressed even in a varied environment.

The application of the afore-mentioned principles to the phenomenon of micrococcal penicillin-resistant provides, at the present, two possible mechanisms. The first mechanism involves a micrococcal adaptive enzyme system in which penicillinase is produced in the presence of the specific substrate penicillin. This has not been entirely confirmed in vitro but has been suggested as a working hypothesis in vivo. If this were the sole mechanism of penicillin-resistant micrococci, it would seem feasible to withdraw penicillin temporarily from our armamentarium. The later reinstatement of the drug might predicate renewed sensitivity via the process of deadaption, at least until the production of new adaptive systems.

A second mechanism entails the selection of a few resistant mutants from a large micrococcal population as a result of the destruction, by antibiotics, of the preponderant susceptibles. This is thought to be a likelier explanation of micrococcal penicillin resistance and is accompanied by suggestive experimental data. Selection permits the survival and multiplication of the resistant strains, with subsequent cross infection to others with a strain which is antibioticresistant.

Penicillin resistance in micrococci entails multiple steps, with a gradual development of resistance over months to years. In contrast, micrococcal resistance to streptomycin, isoniazid, and aminosalicylic acid develops in one rapid step. Highly resistant organisms usually possess more genetic variability. Therefore, if the mechanism of selection is accepted, the temporary removal of a given antibiotic might permit renewed sensitivity on later reinstatement via the process of genetic variability.

Pathogenesis

The production of disease by micrococci is attributed both to their ability to multiply and spread in tissues and to their production of extracellular substances. Among the latter are exotoxin, leukocidin, enterotoxin, coagulase, hyaluronidase, staphylokinase, proteinases, and lipases. The pathogenic capacity of a given strain of micrococci embraces a combination of the invasive properties of the strain and the extracellular factors. The furuncle is the prototype of micrococcal infections. The organisms become entrenched in the hair follicle and porduce tissue necrosis (dermonecrotic factor). Production of coagulase causes coagulation of fibrin around the lesion and within the lymphatics. The limiting wall which is formed is reinforced by the accumulation of inflammatory cells and fibrous tissue. The abscess wall limits the spread of infection but also interferes with free access of antimicrobial drugs. Surgical drainage may be necessary if spontaneous rupture does not occur. The coagulase test is the best criterion for distinguishing potentially pathogenic micrococci from innocuous organisms.

The separation of micrococcal secondary infection from colonization has been clarified by the work of Pillsbury and Kligman. Culture alone is not helpful, since micrococci frequently contaminate broken skin. The reaction of the host to infectious disease produces the manifestation of that disease. Therefore, secondary infection is likely present if large numbers of bacteria and polymorphonuclear leukocytes are present, and especially when the leukocytes have phagocytized the bacteria. The latter is good evidence of body defense. The presence of bacteria without a polymorphonuclear response or phagocytosis indicates mere colonization.

Micrococcal Hospital Infections

The problem of antibiotic-resistant micrococci is most acute in hospital populations. Wysham and Kirby studied micrococcal infections in a general hospital. They divided the 189 patients in their study into 3 groups. Group 1 consisted of 57 patients who had acquired their infection outside the hospital and were subsequently either admitted to the hospital or seen in the outpatient department. The majority of these cases were relatively benign skin infections in adults and were sensitive to antibiotics. As studied by disk diffusion techniques, 40% of the causal micrococci were sensitive to all antibiotics, 35% were resistant only to penicillin, and 19% were resistant to tetracycline, streptomycin, and penicillin. Group 2, of these authors, consisted of 100 patients who developed a micrococcal infection one or more days after hospital admission. Three per cent of the causal micrococci were sensitive to all antibiotics; eleven per cent were resistant only to penicillin; thirty-six per cent were susceptible to chloramphenicol, erythromycin, and bacitracin and resistant to tetracycline, streptomycin, and penicillin; twenty-six per cent were sensitive only to bacitracin, and most of the remaining were resistant to two or more antibiotics. Group 3 consisted of 32 patients who acquired their infections within 60 days after hospital discharge. The antibiotic resistance in this group was similar to that of Group 2. This study demonstrates that micrococcal infections acquired in a hospital are much more resistant to drugs than those acquired outside the hospital.

Micrococci are well adapted for cross infection in hospitals, for the dried organisms may remain viable and virulent in dust, bedding, mattresses, or other fomites for months or years. Micrococci may thrive for long periods in the nasal passages of hospital patients or personnel. Once infection is established the organisms apparently multiply quickly and disseminate in enormous numbers from patient to patient, patient to personnel, and personnel to patient. Thus, there are numerous opportunities for cross infection of antibiotic-resistant micrococci in a hospital.

Goldberg and Masterson obtained nasal cultures of 30 nursing students who recently entered hospital service. They found that only 5% to 8% of the students had penicillin-resistant micrococci prior to hospital service, and 50% of the students had such organisms after four weeks of duty. The primary reservoir of coagulase-positive micrococci is the nasopharynx. Fifty to seventy-five per cent of hospital personnel are nasal carriers of the organism. The nasal carriers are frequently skin carriers of the same strain. According to Wise and co-authors, the incidence of antibiotic-resistant strains of micrococci found in hospital patients is roughly proportional to the duration of time spent in the hospital and to the quantity of antibiotics administered to the hospital population. If a given antibiotic is not used for a period of time the incidence of micrococcal strains resistant to that antibiotic decreases. A decreased number of strains resistant to chloramphenicol (Chloromycetin) was seen, according to Wise and co-authors, shortly after 1951, coincident with a sharp drop in the use of that drug. With the increased use of chloramphenicol in the past several years, we again see a high incidence of resistance. The bacteriology laboratory of the University of Minnesota Hospitals reports chloramphenicol-sensitive micrococci in 63% of isolates in 1952; 61%, in 1954 and 1955, and only 24%, in 1956.

Report of Cases

Case 1.—A white female nurse aged 24, was admitted to the dermatologic service of the University of Minnesota Hospitals on Sept. 15, 1957. Eight days prior to admission she had noted the onset of a painful erythematous plaque on the third digit of the right hand and a transient macular eruption on the trunk and extremities. The digital lesion increased in size, and pus appeared. Twenty-four hours later tender swellings appeared in the right epitrochlear and axillary regions. There had been associated anorexia, 5 lb. loss of weight, malaise, and occasional fever. There was no his-

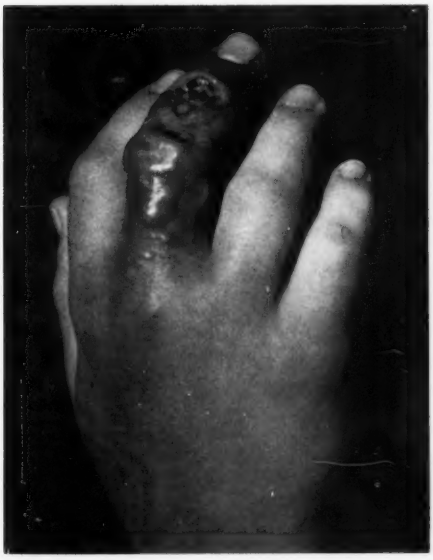

Fig. 1 (Case 1).—Pustular plaque and cellulitis of the right third digit and hand at the time of admission.

tory of preceding trauma. The Mantoux test had been positive since March, 1951, and a chest roentgenogram performed in August, 1957, was read as normal. The patient had been taking no drugs. She had traveled through central California in the summers of 1951 and 1956. In 1951, the patient was repeatedly hospitalized, over a two-month period, for recurrent staphylococcal furuncles.

Treatment, as given by her family doctor prior to hospitalization, consisted of five daily injections of penicillin and streptomycin, 262 drops of potassium iodide (sporotrichosis had been considered), and incision and drainage of the involved area. The lesion increased in size despite these measures.

Physical examination revealed a 2×6 cm. dusky plaque, with central pustular drainage, on the dorsum of the right third digit (Fig. 1). A deep cellulitis extended from the base of the digits to the wrist. The tender affected digit was held in 45-degree ventriflexion. Right axillary and epitrochlear adenopathy was prominent. The temperature was normal.

The differential diagnosis included nocardiosis, tularemia, a resistant micrococcal infection, cat-scratch disease, lymphogranuloma venereum, sporotrichosis, diphtheria, and the primary inoculation syndromes of histoplasmosis, coccidioidomycosis, and blastomycosis.

The Mantoux, coccidioidin, and histoplasmin skin tests were positive (all 1:1000 dilution); the white blood cell count was 15,280, and the erythrocyte sedimentation rate was 16 mm. in an hour. A direct smear and Gram stain of the exudate revealed numerous clusters of Gram-positive cocci, many of which had been phagocytized by leukocytes. Bacterial culture revealed many colonies of hemolytic coagulase-positive staphylococci. The initial fasting blood sugar was high, but repeated subsequent tests were within normal limits. A roentgenogram of the right hand revealed considerable soft-tissue swelling of the third digit without evidence of osteomyelitis. Frei and blastomycin skin tests, potassium hydroxide and acid-fast smears, Löffler's and anaerobic bacteriologic culture, aerobic and anaerobic mycologic cultures (including those at 37 C), febrile agglutination studies, acute and convalescent triple fungus complement-fixation tests, electrophoretic study of the peripheral blood, and a chest roentgenogram were normal.

On the fourth hospital day therapy with high doses of erythromycin and sulfadiazine was started. Because of the subsequent staphylococcal sensitivity studies (resistant to erythromycin and sensitive to oxytetracycline [Terramycin] and chloramphenicol), erythromycin was discontinued and replaced with high doses of oxytetracycline. The areas of involvement localized rapidly, and so on the sixth hospital day incision and drainage were performed (Fig. 2). Fifty cubic centimeters of purulent material was obtained, and an abscess was found to extend from the middorsum of the hand to the distal phalanx of the third digit. Examination of tissue from the abscess wall re-

Fig. 2 (Case 1).—Involved area shortly after incision and drainage.

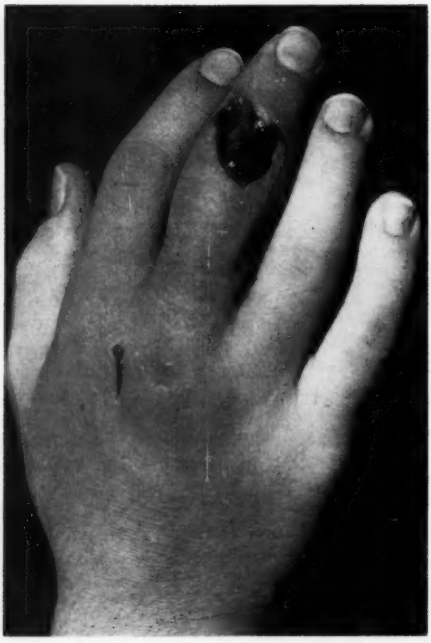

Fig. 3 (Case 1).—Epithelial defect at the time of hospital discharge.

vealed changes of an acute necrotizing inflammation of the skin and subcutaneous tissue. Rapid improvement followed, and so on the 16th hospital day the patient was discharged, with only a 2×4 cm. epithelial defect at the original site of involvement (Fig. 3). Two months later, the defect had healed completely and no residual deformity was noted (Fig. 4). The final diagnosis was a necrotizing micrococcal infection.

The patient in Case 1 was a nurse. Since a high percentage of hospital personnel carry antibiotic-resistant micrococci in their nasopharynx, there is a continual seeding of organisms over the body surface of such persons, especially the hands. The combination of minor trauma, as in the handling of needles and sharp objects, plus the seeding of micrococci affords a likely pathogenesis. That the patient had previously had difficulty inhibiting micrococci was evidenced by the history of recurrent micrococcal furuncles in 1951. The diabetes previously latent may have become overt under the influence of the cutaneous infection. The patient showed few signs of generalized toxicity, despite the severity of the local reaction and the lymphadenitis. There was leukocytosis but no elevation of the erythrocyte sedimentation rate. Chemotherapy helped localize the process and incision, and drainage facilitated drug penetration.

Case 2.—A white woman aged 34 was admitted to the University of Minnesota Hospitals on Nov. 22, 1957. The patient had had recurrent pruritic scaling lesions on the knees for several years. Thirteen months prior to admission she noted erythematosquamous patches, which persisted on her legs and groin, and a red papular eruption on her face, arms, and chest. Seven months prior to her admission, sulfapyridine therapy (oral tablets) was instituted at another medical institution because of the resemblance of the eruption to dermatitis herpetiformis. Marked anemia lead to six blood transfusions. Shortly thereafter, superficial lakes of pus developed in the lesions on the leg. Later, a diagnosis of "multiform erythema" was considered, and the patient was given systemic steroid therapy (hydrocortisone). The eruption improved, but the patient developed overt diabetes requiring special diet and small amounts of insulin. About the same time the patient had sparse bullae and oral lesions. In addition, there was a history of a 20 lb. loss of weight and occasional temperature elevation in the year prior to her admission. The family history was negative for diabetes; the patient's father had died of cancer of the stomach.

Examination revealed slight muscle atrophy of the extremities. Several superficial pustules were present on the hard palate. Erythematous papules were evident on the glabella and alae nasi. A ring of pustules surrounded the angles of the mouth and the area inferior to the lower lip. Postinflammatory pigmentation was evident on the chest. Dark-brown crusted plaques were present on the arms, axillas, groin, and legs. Intermittent and confluent

Fig. 4 (Case 1).—Complete healing (two months after discharge).

lakes of pus were admixed with the lesions on the legs. Crusted, almost gangrenous, confluent patches involved the buttocks.

The differential diagnosis included extensive pustular psoriasis, impetigo herpetiformis, generalized moniliasis, a cutaneous infection associated with an internal malignancy (or other underlying systemic condition), and pemphigus vulgaris or erythematosus.

The hemoglobin was 10.8 gm. % (normocytic normochronic anemia); the white blood cell count was 7800, with a normal differential count, and the erythrocyte sedimentation rate was 43 mm. in an hour. The total serum proteins were 5.4 gm. %, with 2.4 gm. albumin and 3.0 gm. globulin, and the fasting blood sugar ranged between 78 and 98 mg. %. Electrophoretic study of the peripheral blood showed low albumin but normal globulins. A direct smear and Gram stain of the purulent exudate of the leg lesions and the axillas revealed numerous clusters of Gram-positive cocci, many of which had been phagocytized by leukocytes. Bacterial culture revealed many colonies of coagulase-positive staphylococci very sensitive to penicillin, tetracycline, and erythromycin. Examination of tissue from the right knee and the back revealed subcorneal pustules with acute inflammatory cells scattered through the acanthotic epidermis and the corium. Roentgenologic examination revealed an extrinsic mass partially obstructing the second portion of the duodenum.

Fig. 5 (Case 2).—Erythematosquamous patch on the axilla.

Fig. 6 (Case 2).—Discrete pustules and edema of the foot.

Treatment consisted of injections of penicillin and streptomycin, graduated deletion of steroids and insulin, two blood transfusions, Burow's compresses, and, later, ammoniated mercury ointment. During the first week of antibiotic therapy the pustular elements disappeared, and over the following two weeks there was gradual exfoliation of the eruption, leaving postinflammatory pigmentation and slight dependent erythema.

Three weeks later erythematous patches were again noted on the popliteal spaces, thighs, groins, and buttocks; these soon involved the axillas (Fig. 5), back, and perioral area. Discrete pustules appeared on the lower extremities and groin, and edema developed in the dorsal aspects of the feet (Fig. 6). There was no beneficial response to local preparations, including ammoniated mercury ointment, and parenterally administered penicillin. Bacterial culture now revealed coagulase-positive staphylococci sensitive to novobiocin and resistant to penicillin and tetracycline. Examination of tissue from the left axilla and leg now revealed changes compatible with the diagnosis of impetigo.

A short time after the institution of novobiocin therapy, the pustules and edema receded, and there

was a gradual exfoliation of the erythematous patches. Subsequent to study on the medical service, the patient underwent exploratory laparotomy, at which time a large pancreatic mass was resected, together with the contiguous portions of the duodenum and stomach and the gallbladder. It was thought that there was enough pancreatic destruction to account for the diabetes. Examination of the excised tissue revealed a pancreatic islet-cell carcinoma involving the duodenal mucosa. The patient's postoperative course was uneventful. The skin was clear during the postoperative period and has remained so until the time of writing. The patient had gained 40 lb. during this period and was in good health.

The patient in Case 2 was a housewife whose initial cutaneous manifestations simulated dermatitis herpetiformis and later resembled extensive pustular psoriasis, impetigo herpetiformis, pemphigus, or generalized moniliasis. The combination of the laboratory data and the amazingly rapid response to therapy was diagnostic of pyoderma. The increase in antibiotic resistance noted in the later micrococcal infection (acquired in the hospital) compared with the earlier infection (acquired outside the hospital) is noteworthy. The patient had no specific signs or symptoms referable to her abdomen. The gastrointestinal study was undertaken to investigate the possibility of abdominal malignancy predisposing to her peculiar illness. As a result of the extirpation of the islet-cell carcinoma, if complete, it is hoped that the patient will have permanent cure of her recurrent atypical pyoderma.

Summary and Conclusions

The purpose of this report is to call attention to the changing pattern of micrococcal cutaneous reactions.

Some tenets of micrococcal bacteriology and pathogenesis are reviewed with emphasis on possible mechanisms of antibiotic resistance. The rotation of antibiotics, by hospital agreement, has theoretical merit and is worth practical consideration.

Two cases of unusual micrococcal cutaneous reactions are presented. The criteria for secondary bacterial invasion as set forth by Pillsbury and Kligman have been met in both cases.

It seems evident that when one is considering a diagnosis of an unusual micrococcal infection, a complete historical and laboratory study is necessary to distinguish between conditions that may cause similar or identical clinical patterns. The rapid response to the specific therapy indicated by bacterial antibiotic sensitivity studies is of diagnostic value. Predisposing conditions must be searched for much as in moniliasis. Diabetes was present in both reported cases, and a pancreatic carcinoma, in the second case. It is likely that the cutaneous infection will not be permanently cured until the underlying cause is controlled or eradicated.

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Changes in the Skin as a Result of Electric Current

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An electric current passing through the skin produces changes which may be due to the electric current alone. More frequently, however, they are due to a combination of electric current and heat.

Electric burns occur at the point of entrance and exit of the current. This is explained by the fact that the skin offers the greatest resistance to passage of the electric current and thereby causes the generation of heat. Jaffé[1] stated that, owing to this resistance, the most evident changes produced are in the skin.

An electric burn may first appear as a pale crusted superficial ulcer. It may be a pointed or linear elevation of the epidermis, white or gray-yellow in color. The middle of this elevation has linear indentations. At its base and borders the coloration is mostly grayish-black and at times even ruddy. The involved skin feels hard and firm. There is no redness nor pain. Usually the burn is more severe than it first appears because many injured cells do not die for several days. The clinical picture can be complicated further by the electrolytic effect which impregnates metal into the skin at the point of contact with a metal electrode.

The lesions may heal without suppuration and without fever. In areas where the electrical current effect predominates, the hairs remain intact. After a strong high-tension current of prolonged duration, ulcers of the skin extending deep into the tissue, simulating bullet-hole changes, are observed at the point of entrance or exit of the current. In a pure electric burn one rarely finds exudation and hyperemia.

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Kawamura[2] reported 35 fatal and 111 severe electric burns in Japanese coal miners. He admitted that although the lesions clinically were characteristic, they could be simulated by thermal burns. Alexander[3] reported a case in which lesions on the hands appeared as second- and third-degree burns.

Riehl[4] clinically described electric burns as of four types: (1) the superficial, which simply involves the upper epidermis; (2) the erosion type, which goes through the epidermis; (3) the deep necrotic type, which involves the entire cutis, and (4) the bullet-wound type, where there is a vertical tube-like defect in the skin with marginal charring and radiating tears. He differentiated the electric burn from the heat-produced burn by the absence of pain, the deeper involvement, the histologic findings, and the tendency of an electrical wound to heal with a smooth, soft, pliable scar.

Jellinek[5] thought that, although the clinical signs were not pathognomonic, the histologic findings were specific. He reported changes such as honeycombing of the epidermis and cutis, homogenization of the stratum corneum, and bundling and elongation of the epidermal cells with subepidermal vacuolation. Jellinek also described a special characteristic of the effect of an electric current on prickle cells: He showed them to be elongated and parallel to each other like threads, appearing as though tied together in bunches and sheaths. This linear thinning is observed in the nuclei as well as in the cells. Both assume the polarity characteristic of the direction of the current.

Delbanco[6] found that a pin prick caused no sensation of pain when applied to a wound which had its origin in an electric burn. He observed that, although the histo-

logic and clinical pictures separately were not specific, the combination of both was diagnostic. He observed that in the heat-produced burn the elastic fibers were obliterated or torn apart and of a paler staining than normal.

Nippe [7] reported that lightning burns appeared clinically as dry dendritic figures, showing no hemorrhage.

The microscopic examination of electric current changes shows that the stratum corneum is reduced in thickness. The cellular borders have disappeared, and the whole is a homogeneous mass which takes up a heavier stain than the adjacent normal stratum corneum. Between the stratum corneum and the underlying epidermis there are spaces which are divided by septae. The epidermal cutis junction is almost a straight line.

The epidermal cells may retain their normal staining characteristics and show no degenerative changes. Usually, they undergo liquefaction degeneration with elongation and bunching or clumping into sheaths. The nuclei of the epidermal cells are similarly elongated and perpendicular to the surface. Nests of epidermal cells are seen in spaces formed in the cutis. These epidermal cells look like deposits into this altered connective tissue, where they are encapsulated by the tissue. These nests of epidermal cells show a great similarity to the palisade-like cells which have also been reported in experimental burns. The pathognomonic importance of the changes in the prickle cells has

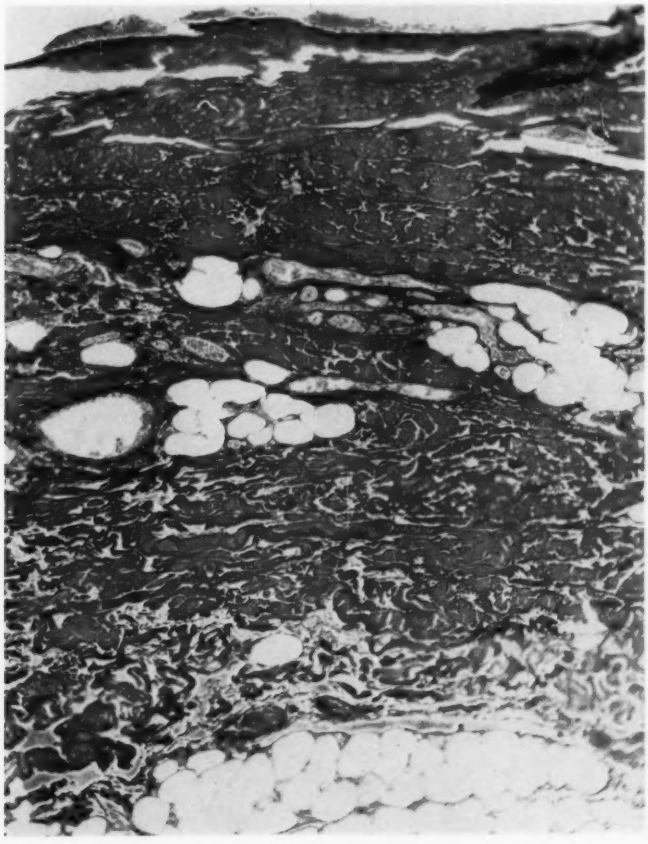

Fig. 1.—Electrocution burn. Photomicrograph. Shows homogenization of connective tissue in cutis, vacuole formation, and absence of cellular infiltrate. Hematoxylin and eosin stain; × 140.

been questioned by some, since similar changes have been seen following the effect of heat.

Microscopic examination reveals a definite denudation of connective tissue of the cutis and a thickening of the individual fibers and bundles caused by passage of an electric current. The collagenous fibers are welded or fused together and form a coarse net-like structure. Homogenization is frequently seen. Weimann [8] and Schridde [9] thought the shrinkage of the cutis in an accordion-like manner was characteristic. There is also a definite tendency for the normally acidophilic connective tissue to become basophilic.

However, directional changes and linear formations involving the epidermal cells are seen not only in electric burns but also in burns caused by molten metal. Charring, dissolving of the connective tissue, and hair-follicle-like overgrowths of prickle cells occur as a result of such heat, just as they do in the case of electric burn. The question of specificity of these skin changes as a result of electric burns is, therefore, debatable.

The effect of the electric current on the skin can be the result of the heat of resistance in the skin to the passage of current. It occurs, therefore, only at the points of entrance or exit of the electrical current. If the current amperage is very high, immediate death of the skin tissue follows. The development of spaces underneath the epidermis is based on the electrolytic changes in the cellular protoplasm, which

Fig. 2.—Electrocution burn. Photomicrograph. Shows dense elastic fiber masses in upper cutis and elastic fibers fragmented in lower cutis. Elastic stain; × 140.

disintegrates from a liquid into a gaseous constituent, tearing the tissues. Hulst [10] reported the action the same for direct and indirect current.

The connective tissue of the cutis is almost unchanged when the current is of high frequency and the amperage is in milliamperes. Where the amperage is more intense, as in household electrical current (up to 30 amp.), the current causes the collagen fibers to become swollen and fused together, so that the cutis appears thinner and reduced in amount.

Report of Study

The specimen studied in this presentation was removed from a youth, age 20, who died three days after accidental electrocution by 5000 volts of high-tension electric current. The skin lesion was 3 in. in diameter on the forearm and was charred. The specimen removed for microscopic examination was sectioned and stained with hematoxylin and eosin. It was denuded of epidermis. The connective tissue fibers in the cutis were fused together in a solid mass which stained dark red. The blood vessels within this mass were thrombosed, and in some areas free hemorrhage occurred into large cavities of the dermis.

On elastic resorcin staining there was an intense increase in elastic-like fibrils which were definitely fragmented. On Mallory staining this degenerated collagen in its more superficial areas was dark red. Deeper in its midportion it was violet, and in its depths, just above the fatty tissue, it stained its normal blue color.

Fig. 3.—Electrocution burn. Photomicrograph. Fragmented increased elastic fibers between larger collagen fibers and bundles. Elastic stain; ×600.

Comment

Hulst,[10] Schridde,[9] and Mieremet [11] were doubtful of the specificity of the stretched bundles of basal cells which Jellinek and Kawamura emphasized. Because both direct and alternating current cause the same lesions clinically and histologically, Hulst doubted that the changes were the result of electrolysis, as did Mieremet. They believed that heat was the cause of the changes. Mieremet passed an electric current through a liver, and the cells arranged themselves parallel to the liver surface and not in the direction of the current. He studied electric burn lesions stained with Van Gieson's stain and showed that instead of taking on a bright red the degenerated connective tissue assumed a yellow-red color. The same changes were observed in skin burns which he produced with a cherry-red cautery. He also observed that the altered connective tissue became basophilic at times and that the changes were due to heat produced by the current and not the current itself. There are certain facts which are prominent. The great amount of elastic-staining tissues which is seen in the upper denuded cutis stained dark red with Mallory's trichrome analine blue stain. This stained red with eosin, having retained its normal acidophilic character. It, therefore, does not fit in with the elastotic degenerated collagen, as described by Gillman, Penn, Bronks, and Roux.[12] In view of the fact that the connective tissue did not stain basophilic in our sections and retained an affinity for resorcinol, yet replaced the normal-staining blue collagen with red-staining fibers on Mallory stain, one must assume that the electric current produced a large mass of elastic fibers. This probably accounts for the noncontractile, smooth scars with which electric burns heal.

Summary and Conclusions

Clinically, electric burns can vary in degree from a superficial erosion to a charred, bullet-like wound.

The histopathological changes in the epidermis are striking. Noteworthy are (1) the production of sheaths of vacuolated spindly cells, (2) the separation of epidermis from cutis, (3) coagulation of collagen of the cutis, (4) cavity formation in the cutis and deposition of nests of epidermal cells, and (5) retention of hair follicles.

The absence of cellular inflammatory reaction is remarkable.

The increase in elastic fibers, together with degeneration of the collagen, is noteworthy in that it is not seen in pure thermal burns. The soft, noncontractile scar in all probability is based on this elastic fiber increase.

William L. M. Martinsen, F. B. P. A., assisted in the preparation of the photomicrographs.

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Clinical Notes, New Instruments and Techniques

Milkers' Nodules of the Nose Resembling Granuloma Pyogenicum

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Milkers' nodules are not very rare in central Wisconsin. The following case is reported because of the unusual location and appearance, which suggested granuloma pyogenicum.

Report of Case

The patient, a 58-year-old white part-time farmer, consulted us early in September, 1957, because of a tumor of his left nostril (Figure). There was a pea-sized globular bluish growth protruding from the left nostril, measuring about 7 mm. in diameter and covered with a thin crust. The lesion resembled granuloma pyogenicum. However, closer examination revealed another lesion over the distal phalanx of his left thumb. This plaque was more flat, solid, and had a purplish color, presenting the characteristics of milkers' nodules (Figure). The patient then recalled that both lesions had appeared simultaneoulsy about two weeks earlier; during the last two months he had milked two cows by hand, both of which had "pox" on their teats.

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From the Departments of Dermatology and Otolaryngology, Marshfield Clinic.

Milkers' nodules of left nostril and left thumb.

The lesions were removed surgically, and microscopic examination of both lesions was carried out by Dr. Hermann Pinkus. The biopsy from the thumb showed characteristic changes of milkers' nodules.

The epidermis is considerably acanthotic, consisting of large, but not particularly edematous, prickle cells, and is covered with a thick parakeratotic layer which lifts up the old normal keratin. The papillae and subpapillary layer are highly vascularized with wide thin-walled capillaries having prominent endothelia. There is an infiltrate of leukocytes and lymphocytes with some monocytes and an occasional plasma cell.

The sections from the nose show similar changes, modified by the different terrain. The surface is covered by a parakeratotic crust; the epidermis is relatively thin, and some papillae reach the surface. Hairs are mostly absent; the follicular lumen is filled with leukocytes. The papillae and subpapillary layer are highly edematous and contain a cellular infiltrate similar to that found on the hand.

Comment

Milkers' nodules of the face are exceedingly rare. Becker [1] in his review found only one such case.

Wheeler and Cawley [2] in their recent review analyzing 28 papers involving 89 cases found only three located on the face (nose 1, lip 1, chin 1). However, it seems that facial lesions in milkers' nodules may be more frequent than hitherto assumed because they are probably not recognized,

owing to the atypical clinical picture. If our patient had not also shown a typical lesion on his finger, we would have missed the diagnosis clinically and probably also microscopically, as Dr. Pinkus believes it would have been difficult to diagnose the facial lesion.

Summary

A case of milkers' nodules with involvement of the nostril is presented. It may be well to consider the diagnosis of milkers' nodules in isolated benign vascular granulomas of the face.

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A Clinical Note on Herpes Zoster

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A perusal of textbooks gives little information regarding the incubation period or the mode of entrance of the virus of herpes zoster into the body. Burgoon et al.[1] quote Kundratitz as follows: "In human inoculation experiments, a period of seven to fourteen days elapsed between injection of herpes zoster fluid and the production of a reaction." An incident which recently occurred in my family related to the above is the reason for this note.

My daughter, aged 4, had sniffles and mild irritability for 12 days and then developed a typical chickenpox eruption. As soon as the eruption appeared, the sniffles and the irritability disappeared. She was given trimeprazine (Temaril *) in a dosage of 2.5 mg. three times a day and at bedtime, which allayed pruritus during the entire duration of the disease. Twenty-four hours later my wife complained of a severe sore throat, and examination revealed an injected pharynx and a swollen uvula. Swallowing was difficult, and it was assumed that she also had edema of the surrounding lymphoid tissue. Capsules containing a combination of tetracycline phosphate complex, 250 mg., and novobiocin, 125 mg. (Panalba † capsules) in a dosage of 1 every three hours were given, as were saline throat irrigations. Seventy-two hours later she developed an intensely pruritic eruption in the second interspace of the left side of her sternum. Examination revealed a grouped papulovesicular eruption on an erythematous base, which was characteristic of herpes zoster. There was no associated pain then or later. A combination capsule ‡ containing Panalba and 6-methylprednisolone (Medrol) was given three times a day for five days, with attendant comfort.

Comment

The occurrence of herpes zoster in an adult (both my wife and I have had chickenpox) following chickenpox in the same household is not commonly observed. Burgoon et al. states, "Cases of chickenpox in persons who are in contact with patients with herpes zoster is not too unusual, while the reverse is less commonly observed." It is possible to pinpoint the incubation period to four days in this particular case. It is also possible to assume that the sore throat and attendant lymphoid edema indicated the upper respiratory tract as the route of entrance of the virus of herpes zoster into the body. Detailed histories of some patients with herpes zoster sometimes elicit a history of vague influenza-like symptoms prior to the eruption; however, it is difficult to estimate the length of time between the prodromal symptoms and the eruption.

Summary

A case of herpes zoster contracted by an adult following chickenpox in a child in the same household is reported. The virus appeared to have entered the body by the upper respiratory route, and the incubation period was four days. Trimeprazine (Temaril) controlled the pruritus attendant to the chickenpox, and tetracycline phosphate com-

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* Chemically Temaril is *dl*-10(3-dimethylamino-2-methylpropyl) phenothiazine and is a product of the Smith, Kline & French Laboratories, Philadelphia.

† Panalba is a product of The Upjohn Company, Kalamazoo, Mich.

‡ This capsule, containing Panalba and 6-methylprednisolone, has no specific name; it was supplied by The Upjohn Company, Kalamazoo, Mich.

plex and novobiocin (Panalba) combined with 6-methylprednisolone (Medrol) was of value in the treatment of the herpes zoster.

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A Method for Sharpening Biopsy Punches

HERBERT L. JOSEPH, M.D., Vallejo, Calif.

Anyone with a modicum of mechanical skill can devise a method for sharpening a punch, but, unfortunately, many of us do not have this ability. Inquiry among dermatologists disclosed that many never sharpen their punches at all, or they have them sharpened occasionally by someone. A few affluent ones just discard their dull punches and purchase new ones.

With use, a sharp metal cutting edge becomes dull when the edge turns over to form a "burr" or "feather." The steel rod used for sharpening carving knives simply straightens up the turned-over edges and thus serves as a quick and efficient sharpener. Similarly, the biopsy punch, which is made of relatively soft stainless steel, is dulled with use when the edge curls inward to form burrs—usually at several places in its circumference. Much of the dulling occurs when the cutting edge strikes other instruments or hard surfaces in handling, especially in washing and in sterilizing. Nurses should be instructed about carefully protecting the cutting edge. A guard is useful and can be made simply from a short length of rubber tubing.

A simple sharpening tool is made from an ordinary carpenter's nail set or center punch of hard steel (Fig. 1). The tip is ground to a taper and polished as shown. It can be made on a "do-it-yourself" basis or by a machinist or gunsmith.* One sharpener can be used on punches of several different sizes, if properly tapered. The sizes of punches to be sharpened must be known in order to make the tool.

The dull punch, with the thin, soft, cutting edge turned in, is sharpened by rotating the tapered end of the sharpener inside the open end of the punch, using firm pressure (Fig. 2). A few rotations turn the burr outward. This is the same principle as the steel rod for sharpening knives. The edge is finished by turning down the outwardly placed burr on a fine stone. The ordinary stone used in the office for sharpening needles serves well. A

* The tool shown was made by Mr. Lyman McCrea, 221 Georgia St., Vallejo, Calif.

Fig. 1.—Sharpener shown with 4.0 mm. punch.

Figure 2

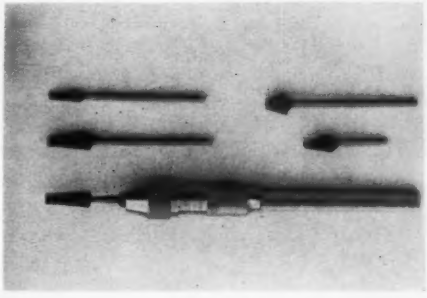

Figure 3

Submitted for publication April 18, 1958.

From the Division of Dermatology, Department of Medicine, Stanford University School of Medicine, San Francisco.

hand lens is useful to examine the cutting edge. A slight "saw tooth" effect cuts as well or better than a perfectly smooth edge. In brief, the tool sharpens by simply forcing the burr outward so that it can be taken off on a stone. A finer edge can be obtained with the use of small-shafted tapered grinding stones† to finish the inner surface of the cutting edge, but this is not necessary. The stones should be used manually in a pin vice (Fig. 3).

607 Carolina St.

† Manufactured by the Dreml Manufacturing Company, Racine, Wis., for use in power tools. These are available in various sizes and shapes at hobby shops or hardware stores.

Gauze Gloves for Wet-Compress Therapy

FRANCIS W. LYNCH, M.D., and HAROLD G. RAVITS, M.D., St. Paul

A "glove" called Dermpak Therapeutic Glove* has been used for applying wet packs in dermatoses of the hand in local hospitals for several years.

It is a 12-ply washed gauze pack stitched together in such a manner that it is used as a glove for the wet-pack treatment of eruptions of the hand. It is obtainable in a large, medium, or small size. These gloves may be washed easily and reused for the same or another patient.

Dermpak Therapeutic Gloves have received wide acceptance by the dermatologists in our area for both hospital and home use. They simplify and expedite nursing, as well as patient instruction, and encourage the performance of proper wet-compress therapy of hands and wrists. Hospital cost accounting has demonstrated that the time saving more than covers the cost of the gloves. It is well known that a patient alone at home cannot otherwise apply compresses well to either hand alone and certainly cannot apply them to both hands.

These gloves are well ventilated so as to prevent maceration of skin. Patients are able to read, smoke, and feed themselves while wearing these gloves. Therefore, treatment has been more effective than with previous methods.

Submitted for publication April 14, 1958.

* Manufactured by Dermpak Corporation, 292 E. 5th St., St. Paul.

Fig. 1.—Gauze glove before application.

Comment

We (and others) have used Dermpak Therapeutic Gloves for hundreds of patients with dermatoses of various types and have found them relatively less expensive and more convenient than other agents and highly effective therapeutically.

546 Lowry Medical Arts Building (2).

Fig. 2.—Gauze glove after application.

Traction Alopecia

ALBERT H. SLEPYAN, M.D., Highland Park, Ill.

The dermatologist has long been aware that persistent and prolonged traction of the hair of the scalp may produce baldness. Many of the more recent writings devoted to the care of the scalp and hair of the female explicitly warn of the necessity of avoiding prolonged traction on any portion of the scalp. Repeated pulling of the hair has been shown to cause inflammation, with its resultant consequences.

Submitted for publication March 19, 1958.

Clinical Associate Professor of Dermatology, University of Illinois College of Medicine.

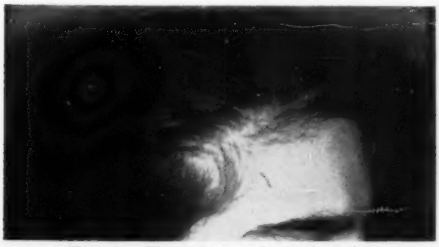

Fig. 1.—Frontal marginal alopecia.

In spite of the repeated admonitions, the pony tail in recent years has enjoyed unusual fascination and popularity among our younger females. It is clear that those who wear the pony tail longer and more tightly drawn are considered more accomplished in the eyes of their contemporaries. It is the prolonged pulling of the hair backward and upward into a smoothly compacted corded hair bundle that has caused loss of hair in many of these persons.

Fig. 2.—Marginal involvement giving postauricular and nuchal area "plucked look."

In the past three years, 24 cases of alopecia of the scalp occurring in young girls wearing the pony tail have been documented. It has been noted that the earliest manifestation is a mild erythema about the follicles receiving the greatest amount of traction. Occasionally some scaling is noted, and not infrequently the patient was seen because "localized dandruff" with itching was suggested by the parent.

In some, minute folliculopustules were evident in these erythematous areas. After several months, along the margin of the hair line or in the part of the hair, occasional hairs appeared missing, giving the area a "plucked" look (Figs. 1 to 3). In well-established cases matchhead- to fingernail-sized oval or linear areas of baldness were seen radiating in the direction of the point of traction. By the time the alopecia was evident the scalp no longer appeared reddened or scaly at these sites. The part of the hair, if involved, may appear irregularly widened by the areas of absent hairs (Fig. 4). At times the hair of the scalp appeared thinned, without evidence, however, of gross baldness. Since many of the youngsters wore bangs, with the part being 1, 2, or 3 in. behind the frontal hair margin, it was not unusual to find evidence of inflammation and even alopecia at these sites. In like fashion the midline part of the scalp and the preauricular, postauricular, and nuchal zones were affected at various times.

When the diagnosis was established, a change of hair style was recommended. Once the pony tail was removed and traction relieved only two patients showed evidence of alopecia after six months. In these two cases the alopecia seemed less extensive than when first seen, but in both persons, however, the remaining alopecia appeared complete.

In one of the girls the pony tail had been worn about 15 months, while the other patient stated

Fig. 3.—Alopecia extending into the temporal area, radiating in direction of traction.

Fig. 4.—Part of hair separating frontal bangs. Note "plucked look," matchhead-sized areas of alopecia.

that she first noted the absence of hair after 3 years. The records of the other patients in this series show that the earliest evidence of alopecia was seen at three months.

In reviewing the literature it became obvious that authors following Sabouraud did not agree that alopecia liminaris frontalis (1931) was a morbid condition of unknown changes. Balina,[1] in 1933, suggested the possibility of traction as an etiologic factor. Sezary and Rabut,[2] in 1937, further suggested a staphylococcic folliculitis following trauma. Spencer[3] showed tightly drawn braids as a causative factor of traumatic folliculitis. Ribeiro,[4] in 1937, suggested the name traumatic marginal alopecia, justified by its localization at some point of periphery of the hair scalp and by its traumatic origin. Costa and Jungueira,[5] in 1943, reviewed the literature extensively and documented clearly a case of traumatic marginal alopecia involving the entire circumference of the scalp and extending well into the frontal area. They concluded on clinical grounds that the symptoms of alopecia liminaris frontalis and traumatic marginal alopecia were identical. It is with this concept that I am in agreement.

However, in their carefully documented discussions, Costa and Junqueira clearly state: "It [traumatic marginal alopecia] may be found in any part of the margin, always, however, being characteristically limited by that margin." If this precise definition were followed, some of these cases of alopecia produced by the pony tail would not fit the criteria for this title, since the pony tail as a causative factor in producing alopecia may produce alopecia anywhere along any line of traction. This traction line need not necessarily be limited to the margins of the scalp (Fig. 4).

It would, therefore, seem logical that since the cases of baldness attributed to traumatic marginal alopecia and alopecia liminaris frontalis all have in common one major precipitating factor, namely, traction, that a less cumbersome and more meaningful title be ascribed to these disorders, namely, traction alopecia. The emphasis in this designation is on the word *traction* rather than on the word traumatic. Alopecia may result from sudden trauma to the scalp with subcutaneous hemorrhage, whereas traction alopecia implies a rather slowly persistent traumatism with its resultant inflammation and sequelae.

Summary

Twenty-four patients with baldness due to the wearing of a pony tail were observed. Of these, two showed evidence of permanent baldness; the others regrew their hair once the traction of the pony tail was relieved. It is suggested that the name traction alopecia be used in describing those conditions which were hitherto designated as alopecia liminaris frontalis, traumatic marginal alopecia, and others in which persistent traction with its resultant inflammation and the sequelae of inflammation can be established.

1893 Sheridan Road.

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An Unusual Case of Dermatitis Factitia

ABRAHAM ZELONY, M.D., Patchogue, N. Y.

Figure 1

A 59-year-old white woman was referred for dermatologic consultation with a tentative diagnosis of petechiae of undetermined origin. The patient had been under psychiatric treatment for several years. As part of her mental state she remained mute, refusing to answer any questions. A history, therefore, was not obtainable.

At the time of the initial examination of this obese woman there were noted on the abdomen 12 to 15 round lesions which were violaceous in color and measured 2 to 8 mm. in diameter (Fig. 1). The lesions were atrophic and slightly depressed. Palpation of the skin of the abdomen revealed the presence of numerous scattered small firm nodules that were intradermal as well as subdermal. Many of the nodules were not in any way associated with the visible lesions. Because the lesions were not truly petechial in nature, and since the lesions did not fit a pattern associated with a specific dermatitis, a diagnosis of dermatitis factitia was entertained.

Submitted for publication May 14, 1958.

Figure 2

An attempt to biopsy one of the lesions was made, but this was abandoned when the cutting instrument touched a rigid object with a metallic click. A small hemostat was then used to remove an ordinary sewing needle. On the basis of this finding it was assumed that the other lesions were also caused by similar foreign bodies. A roentgenogram (Fig 2) confirmed this impression. Apparently, most of the foreign bodies were inserted with no visible skin changes resulting. In a few instances the chronic trauma of the skin by a needle not as yet completely walled off by fibrous tissue resulted in a localized area of atrophy. The atrophic skin had a pigmented appearance due to hemosiderin which appeared after injury to the capillaries.

No doubt this patient still needs psychotherapy. Is any therapy indicated for the dermatologic complaint?

The Brookhaven Medical Arts Building, 4 Schoenfeld Blvd.

Society Transactions

LOS ANGELES DERMATOLOGICAL SOCIETY

S. William Becker, M.D., President
Floralou Kettenbach, M.D., Secretary
The Good Hope Clinic
Nov. 13, 1957

Primary Hypercholesteremia with Xanthomas of Skin and Tendons and Coronary Disease. Presented by DR. JUD R. SCHOLTZ and DR. CRAIG WILLIAMSON.

This 13-year-old boy was first seen in April, 1957. He has had yellow nodules in the skin and tendons and pain in his chest on exertion since the age of 10. All signs and symptoms have increased in intensity in the past year. Lesions are now present on the eyelids, knees, elbows, interdigital webs of hands, and tendons of hands and feet.

Electrocardiographic evidence of severe posterior ischemia in Master's test was consistent with marked coronary insufficiency.

There are marked thrill and bruit over both carotids. Liver and spleen are not palpable.

At the age of 6 years, he had 30 cavities in his teeth. At the advice of his dentist, he has not eaten refined sugar for the past two years.

Biopsy of lesion on knee: Xanthoma.

Blood chemistry: April, 1957: Total lipid 2190 mg. % (normal 450 to 1100 mg. %); cholesterol 856 mg. % (normal 175 to 275 mg. %). ("Serum is turbid but not milky.")

September, 1957: Cholesterol 762 mg. %; β-lipoprotein 96% (normal 50% to 25%).

October, 1957: Cholesterol 720 mg. %.

Treatment has been (1) low-fat diet; (2) corn oil and pyridoxine, 45 cc. daily during August and September; (3) nicotinic acid, 3 gm. daily, started Oct. 15.

Blood chemistry studies of family members show cholesterol levels as follows: sister, aged 13, 321 mg. %; father, 464 mg. %; mother, 330 mg. %; maternal grandmother, 472 mg. %; maternal uncle, 400 mg. %; maternal uncle, 212 mg. %.

Discussion

DR. CLEMENT E. COUNTER: About 8 or 10 years ago, Frederick Urbach presented a most convincing exhibit at Chicago in which he showed that the tumors could actually be reduced, even to complete disappearance, on a diet that contained less than 20 gm. of fat per day. The tumors would recur rather promptly when the patient discontinued such a severe low-fat diet.

Received for publication Feb. 24, 1958.

DR. ESPEY F. CANNON: As you know, Dr. Lever, in Boston, and Drs. Everett, Block, and Curtis, at the University of Michigan, have been doing considerable work on this subject for some time.

A particularly fascinating aspect of their work has to do with the effect on high blood-fat levels of the administration of unsaturated fatty acids, that is, of mixtures of these substances which have a high iodine index. Work has been done in this field by the intravenous administration of emulsions as well as the oral administration of similar compounds. Quantitative studies of blood lipid levels before and after treatment reveal that in a short time—a matter of a very few days—a sharp fall in the original blood levels occurs. The exact mechanism by which this seemingly paradoxical phenomenon occurs is not completely understood, but it would seem to have something to do with the release of lipoproteinase and a reshuffling of the various lipoproteins in their relation to each other.

During the past year or so I have been privileged to witness three cases in which xanthomata disappeared completely within a matter of a few weeks. This was accomplished apparently by supplementing the regular diets with about 60 gm. of Mazola oil daily.

DR. JACK E. MCCLEARY: The occurrence of cardiovascular symptoms at this early age is especially foreboding. I have had the opportunity to follow 11 persons in whom the onset of this xanthomatous eruption occurred during childhood. Of these 11 patients, 6 died of cardiovascular disease, and in 3 of these death occurred before the age of 15. Angina pectoris preceded death in five of these six persons. Of the five patients who are still living, two have angina pectoris and one has survived a myocardial infarction. The three remaining patients who have no cardiovascular symptoms are now between 25 and 35 years of age. In those children who developed angina, death followed within a few months to a few years after the onset of this symptom.

DR. PAUL D. FOSTER: About six years ago, I presented before this society a woman with an average of between 600 mg. % and 800 mg. % of cholesterol. She has been—from time to time—given unsaturated fatty acids and Cytellin, and so far nothing has helped. The cholesterol has

continued to rise. She has been gradually getting worse. The color of her skin has gradually taken on a generalized chamois color with slight thickening. She still is alive, and at the present time she is 47 years of age.

Bullous Congenital Ichthyosiform Erythroderma. Presented by DR. MEYER BERKE and (by invitation) DR. JOSEPH R. TRAUB.

The patient, a girl aged 4, has had a generalized dry nonpruritic scaling eruption present since birth. Periodic episodes of blistering, usually in crops and unrelated to trauma or infection, have occurred, especially on the legs. Her mother has a similar, less extensive, nonbullous eruption. Two sisters, aged 8 and 12, respectively, are unaffected. There is no history of consanguinity of the parents.

There is moderate scaling of the scalp and mild scaling of the face, mainly on the perioral region and the chin. Extensive thickened, brown and gray, keratotic areas are particularly marked on the neck, axillae, antecubital fossae, dorsa of the hands, wrists, lower back, sacral region, buttocks, groin, vulvar region, upper thighs, popliteal fossae, anterior knees, legs, ankles, and dorsa of the feet and diffusely over the abdomen. In the flexural areas the thickening is most extreme and presents parallel rows of rough elevated cornified ridges.

Superficial collapsed and intact bullae and erythematous erosions at the sites of former bullae have been observed on the legs and back. Similar erythematous smooth areas, at sites where the keratin has scaled off, have been present on the trunk and extremities.

The palms and soles are dry but otherwise not affected. Some erythema of the affected areas is present. Perspiration is markedly decreased on all affected areas. There is a small amount of precocious hair growth in the axillae and genital region.

No abnormalities of the teeth or nails have been observed.

Routine hematoxylin-and-eosin-stained sections of a small specimen of skin obtained from the left posterior thigh (nonbullous keratotic area) were interpreted as follows: "There is hyperkeratosis and acanthosis of the epidermis. The granular layer shows a ballooning type of degeneration with large vacuolated and disrupted cells, clear spaces, and increased amounts of large, coarse keratohyaline granules. There is edema and increased mitoses in the stratum Malpighii. There is capillary dilatation in the papillae and upper corium with a mild small mononuclear perivascular infiltrate."

Congenital Ichthyosiform Erythroderma (Nonbullous Type). Presented by DR. MEYER BERKE and (by invitation) DR. JOSEPH R. TRAUB.

The patient, a 35-year-old woman, has had an asymptomatic eruption which has persisted unchanged since birth. One daughter aged 4 (also presented) has a similar, more extensive eruption. There is no history of consanguinity of the parents. The patient recalls having been presented to a dermatologic meeting in Los Angeles, about 25 years ago.

Discussion

DR. LYON ROWE: I should like to suggest the diagnosis of pityriasis rubra pilaris.

Pityriasis rubra pilaris has been classified into two types, congenital and acquired. In the congenital type a severe defect in vitamin A metabolism has been postulated which may be demonstrated by carotene and vitamin A blood levels and by vitamin A absorption tests. It has also been suggested that in those cases where vitamin A metabolism is deranged vitamin A therapy is effective and that in others it is not. Neither of these contentions is substantiated by experience. Cases of pityriasis rubra pilaris of the congenital type have been reported where vitamin A metabolism is normal, according to accepted techniques for such determinations, and where, nevertheless, the use of vitamin A has been clinically successful.

In the literature, also, there is a large variation in the dosage of vitamin A recommended for pityriasis rubra pilaris. In a private communication, Dr. G. H. Curtis related that in three cases of pityriasis rubra pilaris he obtained remission and control with about 400,000 units of vitamin A, cooked and raw carrots, and ¼ lb. butter per day and about 200,000 units vitamin A by injection each week. With this dosage given for months at a time, and in repeated courses over a period of several years, he did not find clinical evidence of hypervitaminosis A.

DR. A. FLETCHER HALL: About 12 or so years ago, a couple of men reported a therapeutic study on the use of saline externally in the treatment of ichthyosis on the theory that in the areas where sweating was diminished the lack of sodium chloride had some bearing upon the clinical skin manifestations. Since then, I have tried brine baths and saturated solution of sodium chloride in an emollient base for treatment of ichthyosis and keratodermic conditions, with considerable success, and I should suggest that for symptomatic relief and cosmetic relief for these little patients brine baths and saturated solution of sodium chloride in something like hydrous wool fat (lanolin) and petrolatum would be worth trying.

DR. HAROLD PRICE: This is an opportunity for Dr. Berke to try to cure these patients with hypnosis. This treatment was reported as being successful in one case.

DR. SAMUEL AYRES JR.: There is something peculiar about the lesions—the accentuation of the borders, the paler centers, and the fact that the mother is certain that some of them have disappeared. Mycological studies should be done. A fungus infection, while unlikely, should be ruled out.

Ataxia-Telangiectasia: A Familial Syndrome of Progressive Cerebellar Ataxia, Oculocutaneous Telangiectasia, and Frequent Pulmonary Infection. Presented by DR. ELENA BODER and (by invitation) DR. ROBERT SEDGEWICK.

Introductory Summary

A group of three children, a white girl 14 years of age, a white boy 13½ years of age, and his sister, 8 years of age, present the main clinical features of a syndrome entity for which the term ataxia-telangiectasia was proposed by Boder and Sedgwick in a preliminary paper based on eight cases and one autopsy, published in the *Medical Bulletin of the University of Southern California* in June, 1957. The main features of the syndrome are progressive cerebellar ataxia, with onset in infancy; progressive telangiectasia of the bulbar conjunctivae, simulating conjunctivitis, and of the butterfly area of the face; frequent sinopulmonary infection, including bronchiectasis, and peculiarity of eye movements, simulating ophthalmoplegia.

The essential components of this familial syndrome are the ataxia and the telangiectasia, the most striking identifying feature being the characteristic telangiectases of the bulbar conjunctivae.

Retardation of statural growth, with significant dwarfing, is a frequent feature. Intelligence is essentially normal, although difficulty with tests dependent upon visual-motor coordination is consistently observed from early childhood and I. Q. scores tend to drop below normal range as the ataxia progresses.

The available pneumoencephalograms give evidence of cerebellar atrophy. The autopsy of a younger sibling of the 14-year-old girl provided microscopic evidence of progressive, apparently primary, diffuse, cortical cerebellar degeneration and of enlarged venules in the cerebellar leptomeninges and white matter, without significant changes in the spinal cord. The autopsy also provided evidence of severe bronchiectasis, pulmonary fibrosis, and mild pulmonary arteriosclerosis.

Ataxia-telangiectasia resists precise classification among the known entities of heredocerebellar ataxia. It is believed, however, that it may be properly viewed as a *fifth* entity in the group of phakomatoses, which presently comprise (1) von Recklinghausen's neurofibromatosis, (2) tuberous sclerosis, (3) von Hippel-Lindau disease, and (4) Sturge-Weber syndrome.

Awareness of the symptom complex of ataxia-telangiectasia will enable the clinician to recognize its varied and seemingly unrelated manifestations as those of a single clinical entity and will eliminate extensive and unrewarding diagnostic procedures.

With the possible exception of a clinical report on a single nonfamilial case published in French, in 1941, there are no reports of this syndrome available to us in either the American or foreign literature. Since the publication of our preliminary paper, however, an as yet unpublished report based on four cases similar to ours and two autopsies was given by Dr. A. Biemond, at the First International Congress of the Neurological Sciences, in July, 1957.

Presentation of Cases

The three children here presented illustrate the symptomatology of the syndrome in different stages:

The *ataxia* is most advanced in the 14-year-old girl, who is nonambulatory. The boy is still ambulatory, but his gait is markedly ataxic. His sister shows a gross swaying of the head and trunk on standing and sitting but no definite ataxia of gait except on turning around or walking a straight line. The ataxia was initially diagnosed as cerebral palsy in both the 14-year-old girl and the boy at a cerebral palsy diagnostic clinic.

The *telangiectasia* is least extensive in the 8-year-old girl, who shows telangiectasia of the bulbar conjunctiva in an early stage, with its characteristic angular location and predominantly horizontal distribution. She presents no cutaneous telangiectasia other than a few subtle telangiectases on the external ears. The oculocutaneous telangiectasia is most extensive in the boy and involves the entire bulbar conjunctiva and some of the palpebral conjunctiva of the lower lids. There is extensive telangiectasia on the bridge of the nose and the butterfly area of the face, particularly on the lower lids. Subtler telangiectasia is present on the external ears, the creases of the neck, the antecubital fossae, and the dorsa of the hands.

The characteristic peculiarity of eye movements simulating partial ophthalmoplegia is present in all three of the children.

Two of the children (the two girls) have clinical evidence of chronic sinusitis and bronchitis and frequently recurring acute respiratory episodes with constant, localized or diffuse, moist crackling rales.

The three patients here presented were examined by a dermatological consultant, Dr. Maximilian Obermeyer, whose findings were as follows: "Telangiectases are present on the sclerae, the sides of the nose, the upper and lower lids, the external ears, and, to a lesser degree, in the folds

of the neck, the antecubital fossae and the dorsum of hands. The skin is dry. On the torso and arms it appears slightly atrophic and taut as if the subcutaneous fat tissues had disappeared. Hyperpigmented macules resembling freckles and atrophic scarring resembling scarring from varicella are scattered on the face.

"The biopsy of the skin above the left clavicle showed the following: On H & E stains the stratum corneus was thickened but loosely adherent. The stratum granulosum was normal to thin and contained some vacuolated cells. The superficial stratum mucosum showed intracellular edema and cells with large nuclei occasionally binucleated. The deeper portions of the stratum mucosum showed smaller cells, the smallest being in the basal layer. One area showed mild intercellular edema. Melanocytes were irregularly distributed in the basal layer which was melanotic. The superficial dermis showed short papillae with collagen a little more dense than normal. The dermis was thicker than normal and contained hair follicles, erectores pilorum muscles, sweat glands and ducts, and, in the deeper portions, fat lobules. The superficial capillaries were dilated and contained blood. Melanophages filled with melanin were seen in the adventitia of the superficial and some of the deeper blood vessels. Elastic fibers stained poorly in the superficial dermis, well in the mid-dermis and poorly in the deeper dermis. Where they stained well they appeared normal. In a few areas they were practically invisible. Stain for hemosiderin was negative for iron. Reticulum stain showed a few fibers, coursing at right angles to the surface. They may have been in or about an erectores pilorum muscle."

Discussion

DR. ELENA BODER: The two essential components of this familial syndrome are the ataxia and the telangiectasia.

Ataxia is the first symptom in all of the cases, having its onset in infancy and becoming apparent, typically, when the child starts to walk, in the present group between 10½ and 13 months. It is clearly an ataxia of cerebellar type, initially of station and gait and later of intention.

Telangiectasia appears to have a later onset than the ataxia, being first detected usually at the age of 4 to 6 years. However, we do not know the exact age of onset of telangiectasia, for none of the patients was seen by us before the age of 6 years. Telangiectasia is first noticed on the exposed portion of the bulbar conjunctiva as fine, bright red, symmetrical, horizontal streaks. The eyes begin to appear "pink" in the sun and when the child has a fever. Usually by the age of 6 or 7 years, the ocular telangiectasia has progressed to simulate conjunctivitis, but it characteristically fades out by the border of the cornea. Like the ataxia, the telangiectasia is slowly and steadily progressive, extending in a symmetrical fashion to the butterfly area of the face, the upper and lower lids, the hard and soft palates, limited areas of the neck, and, later, the antecubital and popliteal spaces and the dorsa of the hands and feet. Although the telangiectasia of the eyes and on the face usually presents a striking appearance as it progresses, the patches elsewhere are usually so subtle that they may be mistaken for fine petechiae. The children with early ocular telangiectasia have also been found on examination to have subtle, previously unnoticed telangiectasia on the external ears. The clinical impression that the telangiectasia is predominantly arterial is confirmed by the fact that it is not visible in infrared photographs.

Susceptibility to sinopulmonary infection, including bronchiectasis, is a frequent feature of the syndrome and was severe enough to cause clubbing of fingers and toes and, ultimately, death in two of our eight cases.

A pecularity of conjugate eye movements not previously described, to our knowledge, in any other neurological entity is another interesting feature of the syndrome. The voluntary eye movements are slowly initiated and interrupted, thus giving an initial impression of partial ophthalmoplegia. On closer inspection, however, it is found that the movements can be completed, given sufficient time. Rapid blinking, resembling that seen in petit mal, occurs, apparently in the effort to overcome the interruption of movement.

Familial incidence is documented with clarity. The eight cases observed by us come from five nonrelated families and include three sets of siblings among the six familial cases.

Ataxia-telangiectasia has similarities with familial hemorrhagic telangiectasia, or Rendu-Osler-Weber's disease. However, the typical telangiectases of Rendu-Osler-Weber's disease are more punctate and different in appearance and distribution from those which characterize our patients and are usually associated with hemorrhagic manifestations. In addition, although some of our patients had a history of nosebleeds, they had never been unusually frequent or severe.

Ataxia-telangiectasia also has similarities with each of the four phakomatoses, particularly with von Hippel-Lindau disease and the Sturge-Weber syndrome. However, it is also sufficiently distinct clinically and pathologically, and sufficiently consistent in its symptomatology, to be properly viewed not as a variant of any of them but as a fifth entity in the group of phakomatoses, which presently comprises, in addition to von Hippel-Lindau disease and Sturger-Weber syndrome, von Recklinghausen's neurofibromatosis and tuberous sclerosis.

All routine blood, urine and cerebrospinal fluid tests have been negative. Special blood and urine tests have failed to show evidence of aberration in iron and copper metabolism. Urinary lead levels have also been normal. Electrophoretic determination of gamma-globulin and recent blood electrolyte determinations in two patients have also given normal values. Additional tests aimed especially at ruling out an inborn error of metabolism are being contemplated and will include urinary amino acid determinations.

Dr. Sedgwick and I would welcome suggestions as to the etiology or pathogenesis of this syndrome, for we are eager to find some therapeutic measure which could arrest the steady progression of the disease in these children. Although the etiology of the syndrome is suggested by its familial incidence, it is still possible that we may be dealing with a deficiency disease or an inborn error in metabolism.

We are especially interested in knowing more about the nature of the oculocutaneous manifestations and, therefore, welcome the opportunity of meeting with the Los Angeles Dermatological Society tonight. We believe that a dermatological evaluation of the oculocutaneous manifestations, which are an essential component of the syndrome, should provide us with valuable clues as to its etiology and pathogenesis.

We should like to raise the following questions:

Does the dermatological picture presented by these children resemble that of xeroderma pigmentosum, progeria, radiation changes, or lupus erythematosus?

What is the significance of the characteristic distribution of the telangiectasia over the exposed portions of the bulbar conjunctivae and the skin in ataxia-telangiectasia? Does it suggest, perhaps, an etiological relationship to sunshine such as has been observed in xeroderma pigmentosum and in another familial entity, known as "H" disease? In "H" disease the relationship to sunshine can be clearly demonstrated, for both its characteristic pellagra-like skin lesions and recurrent cerebellar ataxia are aggravated, or even precipitated, by the patient's exposure to sunshine and are dramatically improved when the exposure to sun is discontinued. In our patients, however, although the telangiectasia is limited to the exposed areas, neither the telangiectasia nor the neurological manifestations appear to be noticeably aggravated or show a more rapid progression during the summer months.

DR. LOUIS WINER: I was impressed by the boy's pinched-face expression, such as is seen in Werner's syndrome. The skin of his face felt tense, suggestive of scleroderma. Werner's syndrome may also involve the eyes with telangiectasia. There is no ataxia in Werner's syndrome. The boy had the spindly extremities which are seen in Werner's syndrome. The girl did not. There is no hyperelasticity of the joints as is seen in Ehlers-Danlos syndrome. I should suggest staining the histologic sections with differential stains to observe any collagen changes, with use of either Mallory's or Van Gieson's stain. The elastic-tissue stain would also be worth while. Histologically, I could see only congestion of capillaries.

DR. ELENA BODER: This observation is both very interesting and accurate. The wasting of the face becomes characteristic in the adolescent period and is associated with the significant retardation in somatic growth and retarded puberty. The wasted face, sunken eyes, and stooping posture give the two older children an appearance of premature aging.

DR. MAXIMILIAN E. OBERMAYER: The involved areas resemble clinically those seen in the atrophic stage of mild generalized scleroderma. The microscopic section which you examined showed principally the pigmentary changes because I removed the specimen from one of the macular hyperpigmented lesions. Dr. Boder and Dr. Sedgwick have done excellent work in singling out this syndrome and should be congratulated on their achievement.

DR. LOUIS H. WINER: Dr. Obermayer is right. If you stain scleroderma sections with elastic stain, the elastic is seen to be fragmented but present in normal amounts. In these children there is a relative, not an absolute, increase in elastic. This is because there is a deficiency of collagenous connective tissue which makes the normal amount of elastic appear relatively increased in amount.

DR. ROBERT W. HELMS: Who is the oldest patient you have had—until what age has he lived?

DR. ELENA BODER: At the present time we are following four patients showing the syndrome, three of whom are presented here today. The other four of our total group of eight cases have died. The oldest patient died at the age of 25 years, of pneumonia complicating measles. The youngest died at the age of 9 years of an "undifferentiated round cell sarcoma of the subcutaneous tissue" infiltrating the right mastoid area and the neck. The two who developed severe bronchiectasis died of pulmonary infection, one at the age of 10 years and the other at 12 years.

We know of only one other similar case in Los Angeles, and that is currently being followed by Dr. Centerwall, of the White Memorial Hospital. Three other unreported cases are being followed by Dr. Douglas Buchanan, of the University of Chicago. Since the publication of our preliminary paper, however, an as yet unpublished report on four patients similar to ours, 9 to 16 years of age, and two autopsies was read by Dr. Biemond, of Amsterdam, at the First International Congress of the Neurological Sciences, in July, 1957.

It has occurred to us that the key to our having observed a relatively large group of children within a narrow range, 7 to 14 years, presenting a distinctive familial syndrome not previously reported as such in the literature, to our knowledge, may lie in the nature of the syndrome itself. It may be that in the decades preceding the development of antibiotics few affected children, being susceptible to severe pulmonary infection, lived long enough to present a fully-developed symptom complex. If this analysis has merit, we anticipate that many more children manifesting the syndrome will soon be discovered and reported.

Dr. Sedgwick and I would appreciate learning of new cases, for we are eager to extend our observations.

Case for Diagnosis: Dermatomyositis; Avitaminosis? Presented by DR. SAMUEL AYRES JR. and DR. SAMUEL AYRES III.

Moniliasis of the Scalp and Nails (Psoriasis?). Presented by DR. JOHN D. ROGERS.

Case for Diagnosis: Granuloma Annulare? Presented by DR. NORMAN E. LEVAN.

Case for Diagnosis: Lichen Planus; Chronic Discoid Lupus Erythematosus; Annulare Lymphocytoma Cutis? Presented by DR. LYON ROWE and (by invitation) DR. SHELDON SWIFT.

Lepromatous Leprosy. Presented by DR. JOHN D. ROGERS.

Argyria. Presented by DR. PAUL D. FOSTER.

Alopecia of Eyelids. Presented by DR. HAROLD PRICE.

Generalized Lichen Planus. Presented by DR. NORMAN E. LEVAN.

Case for Diagnosis: Lichen Planus; Poikiloderma Congenitale. Presented by DR. M. E. OBERMAYER and (by invitation) DR. JACK MACCLEARY.

Atrophoderma Maculatum. Presented by DR. LYON ROWE and (by invitation) DR. SHELDON SWIFT.

Porphyria Cutanea Tarda. Presented by DR. CRAIG WILLIAMSON and DR. JUD R. SCHOLTZ.

Syringoma and Trichoepithelioma. Presented by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.

Cutis Rhombicer Medina. Presented by DR. NORMAN E. LEVAN.

Case for Diagnosis: Hemangiopericytoma; Glomus Tumor? Presented by DR. MEYER BERKE.

Case for Diagnosis: Atopic Dermatitis; Epithelial Nevus; Congenital Ichthyosiform Erythroderma (Nonbullous Type)? Presented by DR. MEYER BERKE and (by invitation) DR. JOSEPH R. TRAUB.

MANHATTAN DERMATOLOGICAL SOCIETY

Paul Gross, M.D., Chairman
Maurice J. Costello, Secretary
Nov. 12, 1957

Pigmented Nevus of Lip. Presented by DR. MAURICE J. COSTELLO.

A girl aged 4 has had a pigmented lesion on the center of the lower lip since birth. The lesion is half-dime-sized, hyperpigmented, sharply circumscribed, and noninfiltrated. The cutaneous and vermilion surfaces of the lip are involved. The patient is presented for suggestions as to therapy.

Discussion

DR. ISADORE ROSEN: I would leave it alone. There is no special indication for interference at this time.

DR. SAMUEL M. PECK: I hate to disagree, but a nevus in that situation has the same indication for removal as one on the palm or sole, because it is open to trauma. We know what can happen to a junction nevus at puberty. There is a cosmetic problem. A beautiful result can be obtained by a good plastic surgeon. I do not believe it needs radical excision but would want to be 100% certain that I am not dealing with an active junction nevus, although it does not look like one.

DR. PERRY SACHS: I feel that a small biopsy should precede therapy. I am confident that this is a cellular type of nevus, but a vascular type is a possibility.

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DR. GEORGE M. LEWIS: I think a small biopsy should be made. If this confirms the clinical impression of intradermic nevus, a satisfactory cosmetic result would follow treatment with solid carbon dioxide. Andrews has publicized this form of therapy in that type of nevus, and while it may take 20 or more treatments the final result usually is excellent.

DR. FRANK C. COMBES: I go along with Dr. Lewis and would recommend subblistering doses of carbon dioxide for a long time. If the result is not satisfactory, plastic surgery can always be done.

DR. ORLANDO CANIZARES: I agree with Dr. Lewis.

DR. ADRIAN BRODEY: I certainly agree that it should be treated with either surgical excision or carbon dioxide, whichever the operator's experience dictates.

DR. JACK WOLF: Solid carbon dioxide is a very satisfactory form of treatment for such pigmented lesions. Trichloracetic acid will frequently remove them in one or two treatments and even may be preferable to solid carbon dioxide. Regardless of the method of treatment, pigmentation tends to recur in situ after a variable length of time.

DR. PERRY SACHS: The microscopic picture may make the use of carbon dioxide or trichloracetic acid inadvisable.

DR. MAURICE J. COSTELLO: This lesion has not increased out of proportion to the growth of the body surface of the child. There is no area of deeper pigmentation, no area of infiltration. Where is the ideal location for a diagnostic biopsy? It is perfectly possible to get different diagnostic reports from two biopsies on the same lesion. Nearly every time I send a biopsy of such a lesion I get a report: Junctions nevus, suggestive of nevocarcinoma; would suggest adequate removal. I told the parents of the child this morning that I would like to treat the lesion with solid carbon dioxide, as suggested by Dr. Lewis and others. It is treated for five seconds at each sitting and if it takes 20 or more, what difference does it make? Otherwise you would have to subject a child of this age to the risks of general anesthesia. A plastic surgeon may obtain an excellent cosmetic result if things go well, but the end-result may be a deformed lip.

Dermatitis Herpetiformis. Presented by DR. ADRIAN BRODEY.

A girl aged 10 was first seen on May 27, 1957, for treatment of a generalized eruption of three years' duration. The dermatosis began with clusters of red blisters on the buttocks. Initially she was treated with antibiotics, hydrocortisone internally, and ultraviolet irradiation. One year previously, in 1956, sulfapyridine therapy had been initiated with good clinical response. Three tablets seemed to control the disease, but when the white blood cell count fell to 4600 the drug was interdicted. The patient was then studied at the Skin and Cancer Unit, where findings on biopsy were not diagnostic. There the patient was treated with antibiotics and Meticorten. She incidentally developed an erythematous eruption from Albamycin.

On first examination there were numerous erythematous vesicular herpetiform and vegetative lesions of the trunk and extremities. The patient was put on a regimen of Meticorten internally and Neosporin ointment. A maintenance dose of 15 mg. of Meticorten a day and of Acthar gel, 80 units weekly, has kept the patient under excellent control.

The patient is presented for discussion of diagnosis and further treatment.

Discussion

DR. NATHAN SOBEL: I agree with the diagnosis. I think it is dermatitis herpetiformis and that it is all right to try Promacetin, maybe in addition to cortisone. Then maybe you can cut down on the cortisone. I have seen some excellent results with Promacetin.

DR. PERRY SACHS: There are pronounced secondary changes which make it difficult to establish a definite diagnosis. While dermatitis herpetiformis may be a possibility, I am unable to establish this diagnosis and would consider seborrheic dermatitis or nummular eczema with secondary changes.

DR. JACK WOLF: The description is a classic one for dermatitis herpetiformis. Obviously she cannot continue to take large doses of steroids indefinitely. Some other approach should be made, and my inclination would be to try other sulfonamide drugs.

DR. FRANK C. COMBES: I think that this girl is very sick. She is very young, and I am thinking of what she will be like 10 or 20 years hence. She should certainly have further study for the possibility of a remote focus of infection and a determination of the sedimentation rate; the polymorphonuclear cells apparently are not doing very well under the sulfonamide drugs, and so I would revert to the sulfones. The worst they can do is give a hypochromic anemia. You have a lot to choose from. With sulfapyridine you might get aplastic anemia; you then switch to sulfones, and the white blood cell count comes up, but you get hypochromic anemia so you switch back again. This cannot be continued indefinitely. The patient should be studied for infection to give her the possibility of permanent relief.

DR. JOHN W. DOUGHERTY: The leukocytes went down to 4700? (Answer: The level went to 4600, and I was not impressed with that.) My impression is that steroids do not do much good in dermatitis herpetiformis.

DR. DAVID BLOOM: While the location is that of dermatitis herpetiformis, the bogginess of the lesions on the legs and the absence of itching do not favor the diagnosis as presented. I have never seen a typical case of dermatitis herpetiformis without pruritus. I feel as Dr. Combes does about therapy. The patient should be studied for a focus of infection. Before steroids are used, any other medication should be employed, possibly also sulfonamides. Steroids should be used as a last resort, in small doses, and for a comparatively short time.

DR. MAURICE J. COSTELLO: Is this patient receiving Promacetin now? (Answer: No.) If this is dermatitis herpetiformis, it is certainly a new form. I have never seen dermatitis herpetiformis which had deep pustular lesions without scarring. It is possible that she has a superimposed infection. It would be interesting to determine whether this girl has a hypogammaglobulinemia which would account, perhaps, for this infection. I would have to depend for diagnosis of dermatitis herpetiformis on what the presenter has observed. There is only one type of dermatitis herpetiformis in which there is no itching. It is the polymorphous pustular type of Brocq, the so-called dermatite polymorphe douloureuse in which the lesions al-

ways begin as vesicles and end as pustules. In my experience, the steroids have been of little value in the treatment of dermatitis herpetiformis.

DR. SAMUEL M. PECK: I am most interested to hear clinicians of wide experience make the statement that dermatitis herpetiformis does not respond to steroids. If you have a severe drug eruption and the patient is exposed to a small amount of the drug, you can give all the steroids you want and eruption will break right through. That means the active antigen is still producing the eruption. We have seen that even with contact dermatitis. Therefore, when I see a picture like dermatitis herpetiformis, even with a high eosinophil count and a high sedimentation rate which are significant and do not respond to steroids, I know we are dealing not with Duhring's disease but with a bacterid with an active focus, and I look for it and find it. There are cases of so-called Duhring's disease that respond dramatically to penicillin or large doses of mycins; they look like Duhring's, but they are bacterids. As far as I am concerned, those are the cases that form the group of nummular eczema. Duhring's disease is always pruritic, and I have yet to see it last any length of time without pigmentation, which was not a feature in this child.

If a patient has gotten a dramatic response to steroids and you discontinue steroid therapy, the whole syndrome comes back.

This patient strikes me as one in whom I would hesitate to make a diagnosis of Duhring's disease. In accordance with a suggestion I made years ago, if this little girl has a low basal metabolic rate, below minus 20%, and you inject Staphylococcus toxoid intradermally, she gets a marked local response; she falls into a special group. Small doses of thyroid and a desensitization with toxoid sometimes lead to good results.

DR. GEORGE M. LEWIS: One of the antihistaminic drugs might be considered to relieve itching.

Case for Diagnosis (Granuloma Annulare; Erythema Annulare Centrifugum?). Presented by DR. JACK WOLF.

A man aged 54 has an extensive, nonpruritic eruption of the trunk and extremities of some seven to eight months' duration.

Blotchy, erythematous areas which impart a sense of resistance on palpation are profusely distributed over the sides of the chest. One small annular lesion, the border of which is neither sharp nor raised, is present on the right. This erythematous blotchiness extends along the inner aspects of the arms and is more pronounced on the left than on the right. The outer aspects are also partially involved. On the inner aspect of the left forearm, near the elbow, the central aspect of the lesion is clear, the periphery mildly indurated. An annular, silver-dollar-sized plaque, more acutely erythematous, is present on the anterior aspect of the left thigh.

Histologic examination of a specimen from the border of an annular lesion revealed a picture which was characteristic neither for granuloma annulare nor for erythema annulare centrifugum and could be compatible with both.

Discussion

DR. FRANK C. COMBES: The patient has one of that bizarre and confused group of dermatoses which I might refer to as erythema perstans. I can tell lots of things I do not think it is, including Darier's erythema centrifugum. We must always think of fixed drug eruption, and we can not disregard that possibility. At the same time, I have seen patients with sarcoid without any more infiltration in the lesion than this. The clinical picture can only guide you in making a diagnosis. One must depend on the histopathologists, and I do not think they would agree in a case like this.

DR. IVERSON (by invitation): Were the lesions negative mycologically?

DR. THOMAS N. GRAHAM: I think a diagnosis of granuloma annulare should not be considered because of the presence of erythema and, also, because of the lack of induration. The eruption resembles erythema annulare centrifugum, but I would also consider erythema perstans.

DR. DAVID BLOOM: I would favor the diagnosis of toxic erythema whether the condition is due to drugs or not. Atypical granuloma annulare is possible, but I would favor the former.

DR. MAURICE J. COSTELLO: I would think it was granuloma annulare. In erythema annulare centrifugum it is rare that you get more than one or two lesions, and occasionally in granuloma annulare you find many. I have a patient just like this now; I finally came to the conclusion that it was granuloma annulare, and it responded to steroids. I think that is worth a trial here.

DR. SAMUEL M. PECK: I was much interested in Dr. Iverson's comment. I have a number of cases with Trichophyton purpureum infections which resemble the findings in this patient. I sent the slides to the Sachs brothers and didn't get very far. Now, there is one way to make a diagnosis even though the organism is very difficult to demonstrate. If you do a trichophytin test, the site of injection reproduces a typical lesion. Do it right into the center of one of the fading lesions and very often it flares up like a brand new lesion. The explanation is that we are dealing with a peculiar allergy to the T. purpureum. Do not disregard the possibility in these lesions.

DR. PERRY SACHS: While it might be difficult to differentiate between various members of the

erythema perstans group, this should not be in the case of granuloma annulare. Further sections or a repeat biopsy may be necessary to arrive at the microscopic diagnosis of granuloma annulare in this instance.

DR. GEORGE M. LEWIS: This reminds me somewhat of a similar case that responded quite well to bismuth injections. In another patient also treated by bismuth there were over 200 lesions of the flat, exanthematic type. When observed recently, the patient reported that she had been well for over two years.

DR. JACK WOLF: This discussion echoes my own thoughts. The eruption is not sufficiently characteristic to allow for a differentiation between granuloma annulare and the erythema group, whether perstans or annulare centrifugum. The possibility of a T. purpureum infection did not occur to me. I shall study the case from that standpoint. My own inclination is a little more toward granuloma annulare than erythema perstans or centrifugum. I told the patient there was a possibility that the eruption would disappear after biopsy, and also that bismuth therapy might cause it to disappear.

Acrodermatitis Pustulosa; Pustular Psoriasis. Presented by DR. JACK WOLF.

A man aged 51 is presented with a pustular and eczematous eruption on the fingers and thumbs, in association with erythematous, scaly, and pustular lesions on the upper and lower extremities.

The patient's past cutaneous history includes a red, scaly patch on the lower part of the back diagnosed as psoriasis some 25 years ago. It disappeared within a year. In August, 1956, he injured his right thumb. About one week later the thumb was lanced and half the nail removed, and penicillin was given by injection. Finally the entire nail was removed. The thumb appeared to be healing but rapidly became infected and was incised once again. Cultures were made, and the patient received both penicillin and the mycins over a period of several months. The thumb improved, only to get worse again. Some time in December, 1956, a few spots appeared on the left arm and on the hands, and this eruption gradually spread to involve the entire body. In January, the antibiotics were stopped. Treatment was purely topical. Blood and urine examinations were normal. Two biopsies were performed at different times, one from the back and one from the thigh, and were compatible with the diagnosis of psoriasis. Despite all therapeutic efforts he did not improve.

I first saw the patient in consultation on April 2, 1957, when he presented a severe, widespread eruption involving almost the entire cutaneous surface. The skin was erythematous, edematous, and diffusely scaly. The axillae were involved and presented the appearance of psoriasis occurring in this location. The nails were all minutely stippled. The distal aspects of the fingers were denuded, exudative, and pustular. With 2% Vioform ointment and Aveeno baths he proceeded to get well except for the involvement of fingers and thumb.

On Sept. 6, 1957, the patient returned to me for treatment of this pustular and exudative eruption. Cultures indicated that we were dealing with an α-hemolytic streptococcus and with a nonhemolytic Staphylococcus pyogenes var. albus. Sensitivity tests indicated that the organisms were most sensitive to Novobiocin, Chloromycetin, and Oleandomycin. Because of the past history, it was felt unwise to give him antibiotics by mouth. Topically there was no response to the indicated preparations. Recently the eruption has begun to manifest itself on the body and is again showing signs of spreading.

Discussion

DR. JOHN W. DOUGHERTY: I believe that it is pustular psoriasis and that the bacteria cultured there could be cultured out of any dermatitis. I do not believe they are causal, but I would try to get rid of them. I would suggest something I have seen work once—large doses of vitamin A.

DR. ORLANDO CANIZARES: Besides what Dr. Dougherty mentioned, I would also investigate for a focus of infection.

DR. THOMAS N. GRAHAM: According to the original report of pustular psoriasis, the pustules are sterile. However, they may become secondarily infected.

DR. ADRIAN BRODEY: I agree with the diagnosis. If Aralen has not already been tried, I would suggest it.

DR. DAVID BLOOM: I believe we are dealing here with a severe type of pustular psoriasis. Dr. Sulzberger presented at the Bronx Dermatological Society a few years ago a case of so-called acrodermatitis pustulosa continua, which was sucessfully treated with sulfapyridine. I would, therefore, try this drug in this patient.

DR. M. J. COSTELLO: I believe it is pustular psoriasis, too. Did you see extensive distribution of superficial pustules? (Answer: No.) Dr. Cipollaro and I followed such a case for a long time, and the patient finally died.

DR. SAMUEL M. PECK: Instead of using Aralen, use APA, and never give more than two capsules. In view of this history I would give antimony potassium tartrate (tartar emetic) intravenously. I have had good results with 1 cc. given very slowly, once a week. Unfortunately, they have stopped manufacturing it. You either have to make the tablets or have them made for you. The APA works very well.

DR. NATHAN SOBEL: There have been reports of Aralen causing psoriasis to spread, and so we should use that cautiously. I would try steroids.

DR. GEORGE M. LEWIS: From the lesions on one or two digits, a diagnosis of acrodermatitis continua might be favored, although the picture as a whole suggests pustular psoriasis. One gains the impression that infection is present here. Antimony potassium tartrate was successful in a few cases. Perhaps γ-globulin would be effective.

DR. FRANK C. COMBES: I agree with the diagnosis as presented. I think pathogentically acrodermatitis pustulosa, pustular psoriasis, Reiter's syndrome, and keratosis blennorrhagica are similar. The response of all to therapy is erratic. At some times improvement follows administration of vitamin A; at others, antibiotic therapy is of help. Focal infections are important, and a search should be made for them. The gallbladder should be x-rayed. I have seen similar eruptions disappear permanently after cholecystectomy. I would also study the liver function in this patient, especially as regards autosynthesis of nicotinic acid.

DR. PAUL GROSS: From this discussion one would gather the impression that acrodermatitis continua of Hallopeau and pustular psoriasis are one and the same disease, an opinion held by many dermatologists. I agree with Dr. Lewis that one has to distinguish between these two diseases. The case presented is one of acrodermatitis continua. Such features as atrophy and complete loss of fingernails, and occasionally lesions of the mucous membranes, do not occur in pustular psoriasis. Disseminated cases of acrodermatitis of Hallopeau should be given special consideration, and the suggestion of Sulzberger regarding sulfapyridine treatment should be kept in mind. I remember a patient with generalized acrodermatitis continua whom I saw in consultation with Dr. Meleney and whose case terminated in death.

The presence of pyogenic organisms in the lesions may be attributed in this case to extensive antibiotic therapy, resulting in invasion by a coagulase-positive Staphylococcus. The lesions of typical acrodermatitis are sterile.

DR. FRANK C. COMBES: If he does have a low γ-globulin, it has been shown that you can get results with antibiotics in one-fiftieth of the dose otherwise required if you give γ-globulin at the same time (Waistren, B. R.: *Antibiotics & Chemother.*, 7:332 [June] 1957).

DR. JACK WOLF: I am inclined to the opinion that the psoriatic state was the result of strenuous antibiotic therapy over many months, and the acrodermatitis continua was primary. Psoriatic erythroderma has followed antibiotic therapy, Aralen, and other forms of treatment. Sulfapyridine was not given on that account. If I give it now and a reaction develops, it will, at least, be on the basis of the best advice.

Despite the fact that Chloromycetin proved best in the sensitivity tests, topical application has done nothing for him.

I rather agree with those who feel that the condition is acrodermatitis continua and that there is an element of impetigo herpetiformis here; it may go along in uncontrolled fashion.

Cutaneous Leishmaniasis (Report of case presented on Oct. 8, 1957). Presented by DR. ADRIAN BRODEY.

The patient has had five injections of Fuadin with no benefit as yet.

Recurrent Erysipelas. Presented by DR. JOHN W. DOUGHERTY.

Leukoderma Acquisitum Centrifugum. Presented by DR. ORLANDO CANIZARES.

Acrosclerosis and Calcinosis Cutis. Presented by DR. ADRIAN BRODEY.

Recurrent Basal-Cell Epithelioma. Presented by DR. ORLANDO CANIZARES.

METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

Edward L. Murphy, M.D., President
Laurence J. Underwood, M.D., Vice-President
Eliot Wolk, M.D., Secretary
Nov. 26, 1957

Idiopathic Poikiloderma Atrophicans Vasculare (Jacobi). Presented by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.

The patient is a 55-year-old Caucasian man who enjoys good health and has noted the gradual progressive development of multiple asymptomatic plaques on the trunk and thighs over the past year. There have been no significant past illnesses.

Located on his trunk and posterior thighs are symmetric large ill-defined plaques, revealing minimal violaceous dusky erythema, fine telangiectases, and minute scaliness. The areas seem atrophic. No infiltration is noted. His skin, in general, is fair. Telangiectasia of the face is noted.

The urine, blood cell count, and blood cell morphology are normal. A scraping was negative for evidence of fungi.

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A specimen taken from the right side of the abdomen reveals mild relative hyperkeratosis with effacement of the rete pegs. The collagen has a somewhat fragmented and edematous, washed-out appearance. There are small vessels surrounded by mild nonspecific infiltrate. In one area in the upper cutis, a denser, nonspecific small-cell infiltrate is noted. The dermis appears atrophic, the sweat glands appearing at a higher level in some fields. On the whole, the pathologic picture here is nonspecific in the hematoxylin-and-eosin-stained sections.

Discussion

DR. CLETE S. DORSEY: Dr. Underwood mentioned in his protocol that the histopathological picture was rather nonspecific. With this I agree. The clinical picture was of very slightly atrophic, somewhat shiny, very slightly violaecous, noninfiltrated, large symmetrical plaques with distinct borders. One needed a good light to see these lesions at all. In the microscopic picture we see reflections of these grossly visible changes, but they, too, are very mild. There is a flattened epidermis, mild hyperkeratosis, very mild infiltration located superficially in the dermis, and mild capillary dilatation. However, the band-like infiltrate hugging the epidermis, the liquefaction of the basal layer, and the degeneration of collagen which are present in classical poikiloderma are not present.

I agree with the diagnosis of poikiloderma clinically but will admit that it is very faint, almost imperceptible poikiloderma. Rather than call it poikiloderma atrophicans vasculare of Jacobi, however, I would label it simply poikiloderma. According to Dr. Montgomery's textbook, Jacobi's original case was probably an example of poikiloderma in association with dermatomyositis. If this is true, there is no basis for continuing the use of this rather ponderous name. Poikiloderma, however, is a useful word. It means something to all of us. It calls to mind a rather distinct type of change in the skin which is found in a number of diseases. In a case such as this one, one may use the word poikiloderma as a starting point and then go on from there to establish as accurately as possible which one of the many conditions which produce this type of change in the skin is responsible for it in this particular instance.

The following classification includes most of the known types of poikiloderma:

1. Hereditary forms of poikiloderma
   (A) Thomson's syndrome (poikiloderma congenitale)
   (B) Rothmund's syndrome (perhaps identical to Thomson's syndrome)
   (C) Poikiloderma which may be associated with other rare or unique congenital ectodermal defect syndromes
2. Poikiloderma secondary to acquired diseases such as
   (A) Scleroderma (including localized scleroderma)
   (B) Lupus erythematosus
   (C) Dermatomyositis
   (D) Lymphoblastomas (including mycosis fungoides)
   (E) Acrodermatitis atrophicans
3. Poikilodermas secondary to physical injury of the skin:
   (A) X-rays, radium, etc.
   (B) Sunlight
   (C) Chronic repeated exposure to heat
   (D) Chronic repeated exposure to trauma
4. Poikiloderma following arsenical dermatitis
5. Poikiloderma for which no cause can be ascertained

Poikiloderma of Civatte is the common telangiectatic discoloration of the sides of the neck which occurs so commonly in persons past middle age and has no place in a classification of true poikilodermas. This classification doubtless does not include all types of poikiloderma which may be encountered. I recall a case of a mycosis-fungoides-like, universal poikiloderma of 30 years' duration which resulted from a mustard gas burn of the entire body sustained by the patient during the first world war.

In this case, I believe that the poikiloderma is secondary to a very superficial morphea. However, one would probably have to follow the patient for a number of years to be certain that some other one of the conditions which have been mentioned was not operating instead.

DR. LAURENCE J. UNDERWOOD: Our patient did not present typical features of well-developed poikiloderma. However, because of the relatively short duration of this disorder, this may be the reason. The plaques are not sclerosed, as is true in active morphea, nor did I consider the pathology or clinical features compatible with morphea or lichen sclerosus et atrophicus.

Case for Diagnosis. Presented by DR. JOHN W. CARNEY and DR. VINCENT P. BURBY.

Case for Diagnosis. Presented by DR. JOHN W. CARNEY.

Sclerosing Basal-Cell Epithelioma (Recurrent). Presented by DR. STANTON B. MAY for therapeutic management suggestions.

Erythroderma. Presented by DR. STANTON B. MAY.

Atrophy of the Skin, Possibly Lichen Sclerosus et Atrophicus. Presented by DR. STANTON B. MAY.

Circumscribed Scleroderma. Presented by DR. IRVING A. LEWE.

Tuberculoid Leprosy. Presented by DR. CLETE S. DORSEY.

Probable Drug Reaction (Due to Milibis or Aralen). Presented by DR. CLETE S. DORSEY.

Necrobiosis Lipoidica Diabeticorium Without Diabetes. Presented by DR. STANTON B. MAY.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILOLOGY

Jack Wolf, M.D., Chairman
L. P. Barker, M.D., Secretary
Nov. 6, 1957

Subacute Lupus Erythematosus. Presented by Dr. Benjamin J. Chester for Dr. James T. Hearin (by invitation) and Dr. Herschel C. Gore Jr. (by invitation).

From: U. S. Public Health Service Hospital, Staten Island 4, N. Y.

The patient is a Negro aged 39.

Complaint: Erythematous, burning lesions of the neck, face, and scalp.

History: This patient first noted lesions on the face in early August, 1957. These were hypopigmented, scaling, and plaque-like and were confined to the bearded area, the bridge of the nose, and over the frontparietal areas of the scalp. When seen two weeks later, the lesions were circinate, somewhat violaceous, and mildly pruritic. At this time lesions of a similar morphology were present over the anterior neck, and the patient was admitted for diagnostic studies.

Description: The lesions on the skin were as described above. The blood pressure was 180/116. A Grade III apical systolic murmur was present, and the eye grounds revealed Grade II arteriosclerotic changes.

Laboratory examinations: A single urine specimen was reported as containing 30 mg. % of albumin. Numerous other urinalyses were within normal limits. Urine examination for Bence Jones protein was negative. Serology was nonreactive. Liver-function studies revealed only a slightly elevated alkaline phosphatase of 8.0 Bodansky units (normal, 5 units). Blood chemistry abnormalities consisted of a hyperproteinemia of up to 9.8 gm. % with globulins representing 5.1 gm. %. Electrophoretic studies of the serum proteins revealed an elevated γ-globulin. A persistent leukopenia in the order of 3000 leukocytes per cubic millimeter with a normal differential count is present. L. E.-cell preparations were negative repeatedly. Erythrocyte sedimentation rate was 30 mm. in one hour (normal, up to 10 mm.). Several stool examinations were negative for ova and parasites. The chest film was reported as showing no significant abnormality.

Biopsy #30598: "In these sections of an inflammatory cutaneous lesion from 'above the left eye' examination reveals a thin, hyperkeratotic, edematous epidermis. There are evidences of degeneration of the deeper epithelial cells. The cutis is edematous and diffusely infiltrated by mononuclear leukocytes which also form a conspicuous focus around what appears to be a coil gland duct. It is my impression that the lesion is probably a lupus erythematosus. Examination of some sections reveal a keratinization within somewhat dilated follicular funnels. Diagnosis: Lupus erythematosus, probably discoid."

Biopsy #30627: "Sections of skin from the 'right deltoid area' reveal a hyperpigmented, edematous epidermis which shows a suggestion of degenerative change in the basal layer. The upper cutis is edematous and reveals an extravasation of red blood cells. There is also a perivascular infiltration of small mononuclear leukocytes. The lesion is a purpuric inflammatory dermatosis, probably an erythema multiforme, but one must consider the possiblity, not of chronic discoid erythematosus, but of a disseminated form of this disease. Diagnosis: Purpuric inflammatory dermatosis. Lupus erythematosus?"

Course: Early in the course of hospitalization, the lesions began to regress, having a dry tenacious scale and a reduction in the erythematous halo surrounding the areas. Four weeks after admission, however, the lesions exacerbated and spread to involve the entire scalp. In addition, papular lesions appeared over the upper chest, across the shoulders and upper back. The patient complained of itching and burning in all affected areas. There was subjective and objective improvement after five days of therapy with meprobamate (400 mg. q. i. d.), 2% hydrocortisone cream locally and cool boric acid compresses. On Oct. 25, 1957, the patient began to complain again of burning, mild pruritus, and pain, and this was accompanied by exacerbation of the skin lesions. The scalp was diffusely hyperpigmented and somewhat violaceous. There were scattered areas of circinate, adherent scaling and excoriations present in the scalp and over the face and neck. Small punctate ulcers were present over the lower lid margins. There was a violaceous hyperpigmentation over the "butterfly" area of the nose, extending over both cheeks and continuous with the scalp lesions and those of the lower face. There was a zone of relatively uninvolved skin around the mouth and eyes. The lower lip was erythematous, scaling, somewhat swollen, and denuded in the central two-thirds. Scattered over the chest, shoulders, upper arms, and back were circinate, scaling to eschar-covered lesions of fairly uniform size (up to 1 cm.). Firm, small, papular lesions were interspersed among the previously described lesions. The tips of both ear lobes were

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erythematous, dry, and scaling. The mucosa within the external nares was violaceous, somewhat thickened, exudative, and excoriated. A single, large, firm, nontender node was palpated near the ear in the posterior cervical chain.

The patient has been continued on meprobamate and states that he finds that cool boric acid compresses offer the most relief, the 2% hydrocortisone cream increasing the burning and pruritus.

Discussion

DR. CARL T. NELSON: I thought that this might have been a case of disseminated discoid lupus rather than the systemic variety. However, if there is sufficient laboratory evidence to indicate systematization, then I think the clinical appearance fits perfectly well with that diagnosis.

DR. PERRY M. SACHS: A superficial study of the sections of both biopsies showed the picture of lupus erythematosus and, I believe, the discoid type.

DR. CHARLES WOLF: From the clinical standpoint, without looking at the face, the grouping of lesions on the shoulders, the back, and the chest appeared to resemble dermatitis herpetiformis. They looked like vesicles that had ruptured or had been scratched, and they were quite grooved, but when I looked at the butterfly arrangement of the erythema on the face then the picture began to clarify itself, and, I believe, although the L. E. cells have not been found, it fits in fairly well with the concrete diagnosis of lupus erythematosus disseminatus subacuta.

DR. JACK WOLF: Is there no one who would like to comment on the relationship between the seemingly discoid variety and the acute systemic variety? There are such instances, and it would appear as though this patient who presents so many small disseminate lesions belongs in this particular category. His general health does not appear to be very good. It is probably this particular type of patient in whom conversion from a relatively benign to a more malignant form of lupus erythematosus is most liable to occur.

Dermatitis Herpetiformis. Presented by DR. H. SHATIN.

From: Veterans' Administration Hospital, Bronx, N. Y.

The patient is a white man aged 61.

Duration: One year.

Location: Soles.

Description: The soles reveal a tender cribriform honeycombed, dry hyperkeratosis. Areas which have been treated with strong keratolytics show a smooth, finely dimpled skin.

History: In the past six years the patient has had several admissions to this institution for a markedly pruritic, vesicular eruption, appearing either isolated or in groups on an erythematous base and disseminated over the trunk and the extremities. Remissions have been achieved following the use of sulfapyridine.

Involvement of the soles has occurred in the past year associated with marked pruritus and tenderness. When the patient was first seen a month ago, in addition to the lesions on the soles, there were again evident patches of grouped vesicles on an erythematous base, extremely excoriated, on the trunk and extremities. These lesions have subsided spontaneously under minimal, nonspecific therapy.

Skin Biopsy #64700: On this admission biopsy material was taken from the soles, and the report is that of dermatitis herpetiformis, the slide showing vesiculation at the dermoepidermal junction with marked eosinophilia.

Discussion

DR. ARTHUR B. HYMAN: I presume the diagnosis was offered on purely histologic grounds in that the cellular infiltrates showed numbers of eosinophils, but eosinophils alone do not establish a diagnosis of dermatitis herpetiformis. The whole clinical picture is strongly against this diagnosis. I suppose we could give it clinically descriptive terms. This is some kind of plantar hyperkeratosis, and there is a picture, the exact counterpart of this, in the 10th edition of Sutton (p. 583) under the name keratoma plantare sulcatum. On all clinical grounds we can exclude dermatitis herpetiformis.

DR. PERRY M. SACHS: Microscopically, there are accumulations of polymorphonuclear cells with some eosinophils in rather discrete masses but not in the papillary bodies. They are intraepidermic, a picture that can be seen in many conditions including dermatophytosis and dermatophytid. I could not establish the diagnosis of dermatitis herpetiformis microscopically or clinically.

DR. CHARLES WOLF: If the feet are examined —and these are the only lesions at the present time—there is a nutmeg-grater-like feel that you get on passing your hand over the lesions. On closer examination you observe hyperkeratotic papules with umbilication. The intense roughness, the hyperkeratotic condition of the entire sole gave me the impression that we were dealing with a case of keratosis punctata. The only difference between this case and a typical case is that the lesions in the typical case are larger but these lesions are so closely aggregated that this aspect of the picture is absent, and therefore my diagnosis on the sole eruption is keratosis punctata.

I would like to ask whether a biopsy was done on a lesion of the soles.

DR. JACK WOLF: Yes.

DR. CHARLES WOLF: What was the report?

DR. JACK WOLF: Dermatitis herpetiformis.

DR. JUAN LARRALDE: It is true that the diagnosis was made on histological grounds, and we frankly have been at a loss to consider this as a case of dermatitis herpetiformis because of the clinical picture. This case presents the clinical picture of keratosis punctata. We presented this case just because we were not completely convinced by the pathologic findings. It is very interesting to hear from the pathologists. That is one interesting fact that I have learned tonight, and I think that the case should not be considered as dermatitis herpetiformis.

DR. JACK WOLF: That is the very point I was going to make. This patient has had several past episodes of disseminated, erythematous, papular, and pruritic lesions which responded well to sulfapyridine. But, by no stretch of the imagination, despite the history of clinically typical, and therapeutically proven, dermatitis herpetiformis, can one consider the cutaneous manifestations present on the soles as those of dermatitis herpetiformis.

There are times when the clinician must of necessity determine whether the pathologic diagnosis is acceptable and consistent with the clinical diagnosis. When the pathologic findings, as in this instance, are misleading the clinician must have the courage to disregard the confusing pathologic picture or at least interpret it on the basis of the total picture, including especially the clinical findings.

DR. ORLANDO CANIZARES: May I close for Dr. Shatin? We have been following this patient for the last six years. We have admitted and readmitted him at the Veterans' Administration, and he has had different lesions, some of them suggestive of erythema multiforme, most of them definitely suggestive of dermatitis herpetiformis. There is no question in our mind; he has that. It has been proved by multiple biopsies and by the response to therapy. Recently this patient developed these hyperkeratotic lesions of the feet. We have found that this picture has been described as part of dermatitis herpetiformis. On that basis, with the suggestive pathologic changes, the diagnosis of dermatitis herpetiformis of the feet was made.

Case for Diagnosis: Multiple Hemorrhagic Hemangioma of Kaposi? Presented by DR. ORLANDO CANIZARES.

From: Veterans' Administration Hospital, Bronx, N. Y.

The patient is a white man (Spanish) aged 27.

Duration: Seven years.

Location: Dorsum of toes, lateral and medial aspects of the feet and ankles with some extension up the legs.

Description: Numerous reddish-brown to brown macules and papules isolated, grouped, and in several areas coalescing to form a reddish-brown plaque.

History: Lesions originally appeared over the mesial aspect of the right foot and have slowly extended to involve the present sites. The lesions at the original site coalesced to form a plaque. A superficial ulceration developed in this area a year ago, healed slowly, and recurred again four months ago following minor trauma. This ulcer has healed coincidentally with radiotherapy to the plaque on the posteromedial aspect of the right foot.

Radiotherapy factors: 100 kv., 1 mm. Al filter, half-value layer 2 mm. Al, 200 r in air, 3 times a week, to a total of 1200 r.

Laboratory data: All studies essentially normal.

Skin biopsy #63976: There is hyperkeratosis and slight acanthosis. There is a mild infiltrate in the upper cutis and mid cutis, essentially perivascular, consisting of lymphocytes and some histiocytes. There is an apparent increase in the number of capillaries, some of which are engorged and show a thickening of the walls and evidence of endothelial proliferation. Free erythrocytes are visible in the cutis as well as intra- and extracellular pigmented material, apparently hemosiderin. Compatible with early stage of Kaposi's sarcoma.

Discussion

DR. ARTHUR B. HYMAN: The histologic picture here shows a mild increase of small vessels in the upper cutis and a nonspecific, noncharacteristic, nonpathognomonic infiltrate such as one would find in many of the hemosiderotic eruptions of the legs. These have gone under many different names which are totally unimportant. I think we all agree by now that there is no necessity of going into their differential diagnosis. Here the histologic changes are similar to those seen in early Kaposi's disease. The flat lesions of Kaposi's disease, when associated with more characteristic lesions, are not difficult to diagnose. But on the basis of the histologic features alone it would be impossible in this case to say more than they are compatible with the clinical diagnosis. This man aged 27 had the lesions for seven years. Kaposi's disease at the age of 20 is most unusual. In a relatively nondescript eruption on the lower parts of the legs, the *histologic* evidence here to support a definite diagnosis of Kaposi's disease is not reliable. Diagnosis should rest on more substantial criteria. I, therefore, could call this case hemosiderosis of the legs.

DR. PERRY M. SACHS: You cannot establish a diagnosis on these sections. The findings show some degree, as mentioned, of superficial telangiectasia, dilated thick-walled blood vessels in the mid cutis, and, also, a great amount of pigment which I presume is blood pigment. As mentioned, such a picture can be found as part of the Kaposi picture. However, as a rule you will find other evidence, even in early lesions, such as small spindle

cells which are not present. I am unable to make a microscopic diagnosis of Kaposi's sarcoma in this case.

DR. ORLANDO CANIZARES: We had a considerable amount of discussion on this case and presented it with a question mark. In the last few years we have seen several cases of what was proved to be Kaposi's sarcoma, which started with these ill-defined pictures, and which were very easy to miss on that basis. I may be prejudiced by those previous findings. This diagnosis was made clinically. The pathologists were willing to go along with it.

Mycosis Fungoides. Presented by DR. BENJAMIN J. CHESTER and DR. HERSCHEL C. GORE JR. (by invitation).

From: U. S. Public Health Service Hospital, Staten Island, N. Y.

Discussion

DR. CARL T. NELSON: For the benefit of the younger members of the audience, I think it would be interesting to have Dr. Chester review this man's clinical course before the diagnosis of mycosis fungoides was established. As I recall it, the diagnosis originally was lichen planus or Atabrine sensitivity. It might be instructive to hear more about this.

DR. JACK WOLF: I will help Dr. Chester initiate this review by saying that I had occasion to see this man many years ago, and at that time he had extensive lichenified areas involving locations in which one finds classic atopic dermatitis. There was the general agreement that the man had atopic dermatitis; no other diagnosis was entertained for a long time thereafter. Gradually the eruption began to spread and changes not associated with atopic dermatitis began to take place. It was then evident that this man had mycosis fungoides.

DR. BENJAMIN J. CHESTER: This patient was first seen at our hospital about nine years ago. At various times when the diagnoses of mycosis fungoides were not corroborated by the histopathologic findings such diagnoses as poikiloderma and hypertrophic lichen planus were considered. The histopathologic picture was highly suggestive of hypertrophic lichen planus in the past. Superficial radiotherapy at that time was not effective. He developed a reticulum-cell lymphosarcoma over the left scapula a few years ago. He received deep x-ray therapy to this area and has not developed any new lesions in this region over an area about twice the diameter of the treated area.

DR. OSWALDO ARIAS: The possibility has occurred to me that this patient may also have a treponematosis, pinta, because of the pigmentation, of bluish color, which is rather unsual in mycosis fungoides.

Case for Diagnosis: A Pigmented, Purpuric Eruption Limited to One Leg (Calf). Presented by DR. J. LARRALDE.

From: Veterans' Administration Hospital, Bronx, N. Y.

The patient is a white man aged 45.

Duration: Since childhood.

Location: Right calf.

Description: There is a well-defined, flat, dark-brown plaque, 10 by 20 cm. in size on the medial aspect of the right calf. The border is irregular and sharp and the upper and lower poles show erythematous macules, small telangiectasia, and powdery scaling.

History: The lesion has been present since childhood, asymptomatic and enlarging gradually over the years.

Skin biopsy #64691: There is a slight lacy hyperkeratosis and flattening of the rete pegs. The basal layer in places appears to show a liquefaction degeneration with slight tendency of the infiltrate visible in the upper cutis to migrate into the epidermis. There is a mild, essentially lymphocytic infiltrate, both diffuse and perivascular in the upper cutis and perivascular only in the deep cutis. There is definite thickening of the walls of the vessels in the upper cutis with a tendency toward obliterative endarteritis and a diffuse red-cell extravasation all through the cutis. The picture is compatible with a pigmented purpuric eruption of the Schamberg type.

Discussion

DR. PERRY M. SACHS: Considering the onset in early childhood, I felt it was a form of nevus. Microscopically, I could not find evidence of a nevus.

DR. JACK WOLF: Can one, by any stretch of the imagination, consider the diagnosis of Schamberg's disease in a congenital eruption occupying one area and showing neither signs of growth nor the development of pigmentation in other locations?

DR. CHARLES WOLF: I might mention a case that I have under observation at the present time, a girl of 10.

DR. JACK WOLF: The case tonight?

DR. CHARLES WOLF: Yes, I am going to make an analogous report.

DR. JACK WOLF: We have not seen the other one.

DR. CHARLES WOLF: I am going to show it to you and tell you the history. It bears out what Dr. Sachs has said. Histologically there is nothing abnormal in the biopsy report. There is nothing in the two areas where the biopsy was performed. The skin is perfectly normal. I am going to show this case at the next meeting to indicate that even with biopsies you cannot always get a picture of

a nevus in the tissue. This case also shows a negative report from the histological standpoint, and so you do not know whether it is a nevus or not, but it looks like one, and it is my opinion that it is that.

DR. ARTHUR B. HYMAN: The color of this lesion should be considered on three possible bases. If this were due to melanin, pigment should be found in melanocytes of the basal zone and/or pigment in the upper cutis. Apparently that was not seen. Or, the color could be due to nevus flammeus, and that should show the dilated vessels in the upper cutis. Thirdly, and most probably, this is presumably some kind of hemosiderosis of the lower parts of the legs. The unusual feature is that the lesion lasted for such a long time, since birth, and I cannot explain hemosiderosis of such long duration in this case.

Perifolliculitis Capitis Abscedens et Suffodiens. Presented by DR. ORLANDO CANIZARES.

This patient was treated one year ago by temporary epilation of the scalp in association with systemic antibiotic therapy and at the same time the sinus tract of the left cheek was treated by radiotherapy (120 kv., 3 mm. Al filter, half-value layer 3.5 mm. Al 100 r three times a week for a total of 600 r).

(This patient was previously presented at the meeting of this Section on Jan. 2, 1957, and is now shown as a follow-up one year later.)

Discussion

DR. ARTHUR B. HYMAN: I think it would be unkind not to congratulate Dr. Canizares on a very wonderful result, in a disease most resistant to treatment. The results of his therapy have been excellent.

DR. ORLANDO CANIZARES: This man had this condition for four years. He had a considerable amount of minor surgery without definite improvement. We have seen several cases of this condition at the Veterans' Administration Hospital. We have used practically any means of therapy that could be used before epilation—opening the sinuses, giving large doses of antibiotics, combining different antibiotics, etc.—with very little improvement, and for that reason epilation was recommended by Dr. Shatin, and the results are very gratifying. He also had a sinus on this side of the cheek. Very often these patients have different sinuses or tracts of similar types of lesions, sometimes on the back or on the buttocks. This patient was given radiation in that area. This apparently reduced the inflammation, and the sinus healed.

DR. CHARLES WOLF: How many areas received the epilating dose?

DR. ORLANDO CANIZARES: I did not do it myself, but I suppose he had the usual epilating technique.

DR. CHARLES WOLF: The epilating dose to one area?

DR. ORLANDO CANIZARES: To the entire scalp.

DR. CHARLES WOLF: As in tinea capitis?

DR. ORLANDO CANIZARES: Yes.

DR. CHARLES WOLF: That is a very good result.

Multiple Hemorrhagic Hemangioma of Kaposi. Presented by DR. ORLANDO CANIZARES.

Discussion

DR. ORLANDO CANIZARES: The interesting feature in this case is that this patient had a nodular lesion, which was purplish-blue in color; he had that lesion removed surgically in another hospital and examined by the general pathologist, and the diagnosis of sarcoma was made, with the recommendation of amputation of the leg. Fortunately, this patient did not agree to have this procedure done and he came to our hospital. We requested the slide, and the diagnosis of Kaposi's sarcoma was made. More typical lesions of Kaposi had appeared on the anterior toe. When he received x-ray therapy, the whole lesion disappeared in a short period of time.

The patient was treated with deep x-ray, 260 kv., Thoraeus filter, half-value layer 2.5 mm. Cu, 50 cm. T-SD; 4000 r to the midpoint (tissue dose) through a two portal cross firing technique. The schedule was divided into two treatment periods a month apart, 2000 r in two weeks in each treatment period.

DR. JACK WOLF: The excellence of the results suggests the advisability of following the dosage schedule outlined by Dr. Canizares rather than the administration of smaller amounts of x-rays, as is usually done.

Erythema Perstans. Presented by DR. BENJAMIN J. CHESTER for DR. JAMES T. HEARIN (by invitation) and DR. HERSCHEL C. GORE JR. (by invitation).

Discussion

DR. JACK WOLF: No comment about the trichophytin?

DR. JAMES T. HEARIN: The response to trichophytin intradermal injections has corresponded somewhat with the findings reported by Dr. Otis Jilson. We have not, however, observed the marked flares of the perstans lesions he reported in his 1954 article.

DR. JACK WOLF: You have not observed any in this case. Has there been any improvement?

DR. JAMES T. HEARIN: He has shown improvement.

DR. JACK WOLF: Do you think it is due to trichophytin?

DR. JAMES T. HEARIN: I cannot say.

DR. CHARLES WOLF: I am rising to controvert the diagnosis. In my humble opinion I think this is a case of erythema annulare centrifugum. The lesion appears centrally and then spreads centrifugally with clearing-up at the initial spot. Some of the lesions have disappeared spontaneously. In erythema perstans the lesions are persistent and stationary. The annular peripheral border is raised which is characteristic of erythema annulare centrifugum.

DR. ALFRED ELIASSOW: I wanted to say the same. I questioned the patient. He stated that these lesions spontaneously disappear, which is against the diagnosis of perstans.

DR. BENJAMIN J. CHESTER: We agree with Dr. Wolf's diagnosis. We used the broader term erythema perstans, which includes annulare centrifigum as one of the group.

Hypertrophic Lichen Planus. Presented by DR. BENJAMIN J. CHESTER for DR. JAMES T. HEARIN (by invitation) and DR. HERSCHEL C. GORE JR. (by invitation).

Tinea Corporis. Presented by DR. JUAN LARRALDE.

Keratosis Follicularis (Darier's); Acne Vulgaris. Presented by DR. JUAN LARRALDE.

Lepromatous Leprosy. Presented by DR. BENJAMIN J. CHESTER for DR. JAMES T. HEARIN and DR. HERSCHEL C. GORE JR. (by invitation).

Chronic Benign Familial Pemphigus. Presented by DR. BENJAMIN J. CHESTER and DR. LEONARD BROWN (by invitation).

Multiple Hemorrhagic Hemangioma of Kaposi. Presented by DR. O. CANIZARES.

Multiple Hemorrhagic Hemangioma of Kaposi. Presented by DR. O. CANIZARES.

Mycosis Fungoides (Bathing Trunk Area). Presented by DR. BENJAMIN J. CHESTER and DR. LEONARD BROWN (by invitation).

NEW YORK DERMATOLOGICAL SOCIETY

J. Lowry Miller, M.D., President
Frank E. Cormia, M.D., Secretary
Oct. 22, 1957

Carotinemia. Presented by DR. WILBERT SACHS.

An 18-month-old child was seen in January, 1957, for yellowness of the skin. Because of celiac disease, the diet contained an abundance of carrots. The skin had an intense yellow tone, especially pronounced on the palms and soles.

A week ago the child was seen again. The mother said that the entire process had disappeared when the diet was corrected. However, for some reason, the child had again received carrots for the preceding few weeks, and the skin had again become yellow.

Discussion

DR. E. F. TRAUB: Does the condition ever cause any harm? If the diet was essential, was it necessary to discontinue it?

DR. FRANK C. COMBES: What interests me is how the child and others similarly affected give evidence of oversaturation with carotene but never have any indication of vitamin A toxicity. Is there in these cases an added inability to convert carotene to vitamin A? This may be an additional cause, besides the excessive ingestion of provitamin A. Can the presenter tell me if this child is capable of converting carotene to vitamin A.

DR. GEORGE C. ANDREWS: I do not know whether carotene studies were made on the patient's serum, but it would be interesting to know the state of his liver function and whether he can convert carotene into vitamin A as well as a normal person can.

DR. CARL T. NELSON: The defect in patients with celiac disease seems to be in the absorption of fat-soluble vitamins. I am not aware of any defect in the conversion of carotene into vitamin A in this disease.

DR. FRANK E. CORMIA: I think Dr. Combes' question is well taken, but there is apparently no evidence of toxicity. I do not believe that carotene is converted to vitamin A too well in this situation.

DR. MAURICE J. COSTELLO: I understand that carotinemia in demonstrable degree is not uncommon in infants under one year. They may have some difficulty in converting carotene into vitamin A, as Dr. Combes mentioned.

DR. WILBERT SACHS: When I first saw the child, I was told that the pediatrician thought it was jaundice. He may have done liver function tests, but I do not know about that. The mother gave me a definite history of celiac disease made by several pediatricians, but she says tonight that some pediatricians doubt that he has it. It is not a question of diagnosis but of diet. After stopping the ingestion of carrots and squash, the color disappeared.

Case for Diagnosis (Dermatitis Factitia?). Presented by DR. GEORGE M. LEWIS.

A housewife aged 37 noticed a raised, itchy area on the left side of the back in May, 1957. After a time a crust developed. When this fell

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off, an open sore was noted. Her physician prescribed various ointments, some of which were irritating. She also expressed a reaction to adhesive tape.

Tissue removed from the edge of the ulceration was reported by the local pathologist to show mycosis fungoides. There has been some healing recently from application of Neo-Cortef ointment.

There is an irregularly outlined ulceration covered with exudate. The border is not elevated. No infiltration can be detected. The surrounding skin shows a pigmented, erythematous, slightly elevated eruption thought to be at the site of the adhesive plaster.

Discussion

DR. WILBERT SACHS: I saw the slide only for a moment, and, in my opinion, there was no mycosis fungoides. The process is a deep one, in the fat. I made a guess of the possibility of Weber-Christian's disease. Clinically, I think a roentgenogram of the ribs should be taken even though the slide did not show the type of necrosis that would be an extension from the rib.

DR. MAURICE J. COSTELLO: I doubt that this area, the size of a palm and sharply marginated, could have been caused entirely by adhesive plaster. Sometimes you will find a tumor in early mycosis fungoides. That diagnosis is probable.

DR. FRANK C. COMBES: Clinically I cannot see any resemblance to mycosis fungoides, but we have to rely on the histopathology. I would like to suggest panniculitis and Darier-Roussy sarcoid plus dermatitis venenata. The patient has used a number of medications including Furacin, a potent sensitizer.

DR. G. C. ANDREWS: The area of dermatitis did not seem infiltrated. It is probably a contact dermatitis from Furacin ointment. The lesion is sharply outlined and localized. I do not think she has mycosis fungoides clinically. I see no tumor, no infiltration, and no other clinical evidence of that disease.

DR. J. LOWRY MILLER: This week I saw a patient who for six years has had a chronic contact dermatitis limited to the area covered by his shorts. Repeated biopsies from this area have been done. One read by Dr. Machacek was diagnosed as mycosis fungoides from a tumor-like lesion, although the patient still has a classic, typical contact dermatitis. I think we would still have to consider the diagnosis of mycosis fungoides in this case.

DR. WILBERT SACHS: There was no suggestion of epithelioid cells or tubercle formation whatsoever that I could see. It is not a tubercular process.

DR. G. F. MACHACEK: As she has an ulcer which, of course, will confuse the picture, I can understand why the pathologist was puzzled. The reaction in the deeper portions was all of a homogeneous variety, all mononuclear cells. Chronic banal inflammation could give that picture, but I would think of mycosis fungoides as a remote possibility.

DR. FRANK E. CORMIA: The patient could have panniculitis, as suggested; however, panniculitis as an isolated symptom and without constitutional reaction would be unusual. Against the presence of a tumor is the lack of infiltration around the ulceration, as pointed out by Dr. Andrews. For the same reason, mycosis fungoides seems improbable. I think Dr. Traub has the best idea—to clear up the secondary dermatitis. I would then apply occlusive dressings.

DR. CARL T. NELSON: At present, the patient seems to have a chemical ulcer. I do not know what is underlying it, but certainly the possibility of a sinus tract from the pleura or rib is worth looking into.

DR. GEORGE M. LEWIS: I certainly am still in doubt as to the exact mechanism of production of this ulcer. The patient is said to be rather a nervous person. She has a few other excoriations on the skin and apparently did traumatize the area in this region. She is known to be sensitive to adhesive plaster, and she has pigmentation on the leg from an earlier dermatitis. This sensitivity was known and yet adhesive plaster was applied anyway. Then came applications of Furacin, and furthermore, a doctor probed the area. Whether the patient herself or the doctor is responsible for the trauma, and whether it is due to a chemical or to a sensitivity, I think there is an element of artifact in this lesion. The suggestion of an x-ray picture of the chest is a good one.

(A radiograph failed to show any underlying bony disease.)

Toxic Bullous Eruption (Pemphigus?); Result of Treatment. Presented by DR. FRANK C. COMBES.

A boy aged 13 was first treated by me on Nov. 25, 1951. He had been previously presented before this society in November, 1951, by Dr. Cipollaro of whom I requested the opportunity to treat him. In June, 1949, the patient had developed a universal bullous eruption. He was hospitalized and given various treatments without much benefit until early in 1950, when he was given corticotropin (ACTH) for a month, with prompt improvement. However, on its discontinuance, the eruption immediately reappeared. When seen in November, 1951, he had a generalized, crusted, bullous dermatosis involving most of the trunk, face, scalp, and extremities. The palms and soles were free. The bullae were flaccid, appearing initially on normal skin, and the crusts were centrally attached, purulent, and hemorrhagic. There was no pruritus, but the involvement was so extensive

and severe that the patient had to be carried. The Nikolsky sign was positive. The mucous membranes were not involved. At that time findings on examination of the blood were as follows: erythrocytes 4,830,000; hemoglobin 98%; color index 1.02; polymorphonuclear cells 30,850 per cubic millimeter; total eosinophils 6020; polymorphonuclear cells 36%; lymphocytes 38%; mononuclear cells 6.5%, and eosinophils 19.5%.

Bacteriologic studies were done on the flora from the nose, throat, and feces. From his nasal cavities Streptococcus pyogenes was isolated. There were also many enterococci and pathogenic staphylococci. Besides these organisms, from his tonsils we isolated Streptococcus salivarius. The same streptococci were isolated from the middle ear and stool. In these two latter locations, a large number of Proteus vulgaris were found. The growth of that organism in the bowel was so profuse as to obscure all streptococci. The Staphylococcus which is his principal pathogen is sensitive only to chloramphenicol and bacitracin. The P. vulgaris and enterococci likewise are highly sensitive to chloramphenicol and partially or completely resistant to other antibiotics, except that the enterococci are also sensitive to penicillin.

The patient was given 1 gm. of Chloromycetin daily almost continuously until April, 1952, with several fortnightly interruptions. He also received cortisone intramuscularly three times weekly and an autogenous streptococcal antigen prepared from the bowel. In addition he was given 1 gm. of Panthenol daily and 2 mg. of epinephrine in oil three times weekly, intramuscularly.

The eruption varied in intensity, but there was overall improvement. During April and May, 1952, carbarsone, 250 mg., was given daily, with no benefit. From May, 1952, until March, 1953, repository corticotropin injection (ACTH gel) was given weekly. Insulin was started daily in October, 1952, and continued. By early 1953, the eruption was much sparser and had changed in nature. The bullae were few, but there was a distinct urticarial and papular element with many parakeratotic vegetative patches, especially over the trunk. Sulfapyridine was substituted for the ACTH and was followed by prompt improvement both subjectively and objectively. This was discontinued in October, 1953, because of lack of further improvement. Since then the patient has been free of any eruption except for some slight erythema and crusting on the flush areas of the face. Blood cell counts since February, 1953, have been essentially normal.

During the winter of 1953 and the summer of 1954, he received monthly injections of antigen and continued to improve. In mid-August, he sustained a severe sunburn, and lesions clinically typical of lupus erythematosus discoides developed over the flush areas of the face, while new bullae appeared on his hands. The latter subsided spontaneously, but the lesions on the face persisted. Treatment for this included mercury oleate ointment locally, fresh pineapple juice in hydrous wool fat, Florinef, Vioform, pancreatin, and Marsilid. Internally he has received sulfapyridine, Panthenol, liver, asorbic acid, vitamin A, Atabrine, Plaquenil, Aralen and intravenous gold sodium thiosulfate, in addition to his vaccine antigen. Best results followed Vioform cream locally and Marsilid internally, but I do not ascribe his improvement specifically to either or both these medications.

I interpret the facial lesions as pemphigus erythematodes, especially since biopsy done in 1952 showed pemphigus vulgaris.

At present and for the past three months the patient's skin has been normal, except for a few comedones. The Marsilid was discontinued in early July, and he is receiving no treatment.

Discussion

DR. MAURICE J. COSTELLO: I saw the patient some years ago and never saw such a severe eruption. At that time it looked just like pemphigus foliaceus. I never thought he would recover. Whether there is a relationship between the treatment and the result and whether any one thing was responsible or all of them together is questionable.

DR. L. P. BARKER: Puberty may have had something to do with it.

DR. GEORGE M. LEWIS: I suppose androgen therapy is the one thing he had not had. (DR. COMBES: He did!)

DR. WILBERT SACHS: I remember the patient when he was presented by Dr. Cipollaro, and the result is remarkable.

DR. FRANK C. COMBES: I think this patient illustrates the fact that the specific distinguishing characteristics between pemphigus vulgaris and dermatitis herpetiformis are quite obscure and indefinite. One cannot draw a definite line which divides all cases. I have seen many diagnosed as pemphigus which in my opinion possessed all clinical and histological features of that disease, but eventually they all changed so that one could only make a diagnosis of dermatitis herpetiformis. These cases initially fail to respond to sulfapyridine but later (many months or years) response may be excellent.

Case for Diagnosis (Dermatitis Herpetiformis?).

Presented by DR. J. LOWRY MILLER.

A healthy man aged 27 has been complaining of an intensely pruritic eruption of the upper and lower extremities and the buttocks, of six years' duration. No treatment has been of avail; it has

included Kwell ointment and Promacetin, 3 gm. daily.

There are pea-sized, bluish-brown, excoriated papules on the thighs, legs, arms, and forearms. Over the sacrum there is some grouping of lesions.

All laboratory studies have been essentially negative. One biopsy specimen from the buttocks was diagnosed as chronic dermatitis. A second, from the arm, showed an epidermis with focal hyperkeratosis and focal parakeratosis. There was irregular acanthosis with prolongation and merging of the rete pegs. In some areas the dermal papillae extended to near the surface and contained prominent capillaries. Within the dermis, there was a chronic inflammatory infiltration which was most abundant in perivascular locations. At one point the epidermis was completely denuded, and the surface of the dermis at this point contained an acute inflammatory infiltrate. At the site of an adjacent lesion, there was an intraepidermal bulla which contained a few cells and showed no acantholysis. The diagnosis was chronic dermatitis.

Discussion

Dr. L. P. Barker: At present this patient presents a dry skin with many excoriations. I would suspect a contact dermatitis from his clothing or chemicals used in cleaning them. Emotional pruritus, however, cannot be discounted. I think sulfonamide drugs are contraindicated at this time.

Dr. Herbert J. Spoor (by invitation): I wonder how much this man is drinking. For a young man he seems very paunchy. There is a possibility of folliculitis or of a Staphylococcus infection.

Dr. George C. Andrews: The man said the eruption began in Korea and that he had diarrhea. Possibly he had amebic dysentery. He should have a stool examination, done carefully on a warm, fresh specimen.

Dr. Frank E. Cormia: Dr. Andrews' suggestion is excellent. I thought the only primary reaction present was folliculitis. In addition there were many excoriations. I do not think the idea of a psychosomatic factor is so far-fetched. The man has been in the Army for a long time, and it is possible that deep-seated emotional problems are present.

Dr. George M. Lewis: I accept the diagnosis of dermatitis herpetiformis as a good possibility although not proved. The grouping is not as evident as it might be, and there is not quite enough atrophy and pigmentation, but the lesions over the buttocks are more suggestive of dermatitis herpetiformis than of folliculitis.

Dr. Carl T. Nelson: I think this is a happy man who by his own volition has spent 13 years in the Army and who happens to have dermatitis herpetiformis.

Dr. Wilbert Sachs: It is my impression that the histologic diagnosis of dermatitis herpetiformis is not too difficult and if it could not be made on two biopsies, this fact would be greatly against a diagnosis of dermatitis herpetiformis. It may be some other form of neurodermatitis, as Dr. Traub suggested—papular or nodular—which would go along with that picture.

Dr. Maurice J. Costello: I have never yet seen a patient with dermatitis herpetiformis on whose skin you were not able to demonstrate a vesicle the size of a pea or smaller, at one time or another. I would agree with the diagnosis of generalized papular disseminated neurodermatitis. The eruption may be related to psychic factors, as mentioned.

Dr. Frank C. Combes: I have never seen a patient with active dermatitis herpetiformis, not under treatment, who did not have eosinophilia. It is a requisite to diagnosis. I would also expect at least 1% or 2% myelocytes in the blood smear. To establish a diagnosis in this case, I would raise an artificial blister and examine its content for eosinophils and acantholytic cells. I would also do a biopsy on this artificial blister. I would give the patient potassium iodide internally and look for any exacerbation of lesions. I would also suggest a stool examination for intestinal parasites. I have seen amebae produce dermatoses similar to this.

Dr. Wilbert Sachs: I do not see how a blood cell count would help as all the diagnoses mentioned here would give you a high eosinophilia.

Dr. Frank C. Combes: But a normal count would be extremely significant in excluding dermatitis herpetiformis, pemphigus, and many intestinal parasites.

Dr. J. Lowry Miller: He has not been hospitalized, and for that reason, we have not been able to carry out many of the suggestions made tonight. At times the eruption has looked considerably more like that of dermatitis herpetiformis, with grouped lesions, but it has never been a typical case. Repeated blood cell counts have never shown more than two or three eosinophils. He is now being transferred to Germany and is very much worried about his eruption because he feels it will interfere with his Army career. He does not strike me as a neuropathic person.

Granuloma Annulare. Presented by Dr. Leslie P. Barker.

An attorney aged 43 was previously presented before this society in November, 1956, with possible diagnoses of granuloma annulare, acne keloidalis, lichen planus, or tuberculid. At that time, there were many follicular, split-pea-sized, raised, firm red papules on the nape of the neck

and a few flat-topped, shiny papules behind the ear. The eruption had been present for 20 years and had not responded to various local medications, radiotherapy, or local injections of hydrocortisone. Biopsies of the follicular papules and the flat-topped papules were more in favor of acne keloidalis than any of the other diagnoses considered.

Since the presentation a year ago, the patient has developed new lesions on the cheeks and forearms. Those on the forearm vary in size from 0.5 cm. to 2 cm. and are round or oval, firm, elevated, red lesions with nodular, raised borders. Some of the nodules have a yellowish tint. The facial lesions are firm, raised, red papules or nodules which lack the definite nodular borders.

Blood cell counts and urinalyses have been normal. Biopsy specimen from a nodular lesion on the forearm showed the picture of granuloma annulare.

Discussion

DR. FRANK E. CORMIA: I think we have to accept the presenting diagnosis. The lesions on the forearms certainly look like granuloma annulare, while some of those on the back of the neck do not. There may be a keloidal element. Possibly a young enough lesion was not taken for biopsy. Ordinarily, local injections of hydrocortisone are a good method of therapy. However, I understand that he has had many such injections without benefit.

DR. GEORGE M. LEWIS: I agree with the diagnosis of granuloma annulare. In a similar case, a series of bismuth injections finally brought about a cure.

DR. CARL T. NELSON: One or two of the lesions on the arms suggest granuloma annulare. The area on the back of the neck still does not look like granuloma annulare to me.

DR. WILBERT SACHS: I think there is little question as to the diagnosis on the forearm or chin of granuloma annulare microscopically. Probably the whole process is. However, if one of the lesions on the back of the neck is taken for biopsy and it shows the same process as before, we would still have to entertain a diagnosis of acne keloidalis and the possibility that this patient has two diseases.

DR. MAURICE J. COSTELLO: The lesions on the forearms are those of granuloma annulare, as are also the majority of the lesions on the neck. Certainly he has interspersed with those some lesions of folliculitis keloidalis—there is no question about that—and in that disease I think refrigeration with carbon dioxide snow is the best treatment. I have a patient who has been treated with bismuth. The response of granuloma annulare to bismuth is irregular as it is to the other drugs mentioned. I administered Meticorten to my patient, 5 mg. q. i. d. The patient had arthritis which gave us an added reason to use that drug, and the result was good. I would advise that therapy.

DR. FRANK C. COMBES: I agree with the diagnosis of granuloma annulare for the lesions on the forearms, and probably those on the back of the neck are the same thing. As far as treatment is concerned, as Dr. Costello says, the response is erratic. One method of treatment which has not failed yet is grenz-ray therapy, but you may have to give enough to produce telangiectasia.

DR. WILBERT SACHS: Do I understand that you get sequelae from grenz rays?

DR. FRANK C. COMBES: Yes, grenz-ray sequelae. These are similar to those following conventional x-rays except that we never see keratoses or epitheliomas.

DR. HERBERT J. SPOOR (by invitation): I would suggest cortisone ointment applied with mild massage and occlusive dressings.

DR. J. LOWRY MILLER: Do you feel you get absorption of cortisone?

DR. HERBERT J. SPOOR (by invitation): I think it has been proved by evidence before the Food and Drug Administration.

DR. MAURICE J. COSTELLO: I suggested Meticorten not for the acne but for the granuloma annulare.

DR. L. P. BARKER: I have repeatedly injected hydrocortisone solution into the papular lesions on the neck without improvement. Ten days ago, the lesions on the left forearm were injected. They have shown some improvement.

Epidermolysis Bullosa. Presented by DR. FRANK C. COMBES.

Dermatitis Herpetiformis Partially Controlled with Diasone. Presented by DR. CARL T. NELSON.

Case for Diagnosis (Neurofibroma; Hemolymphangioma with Fibrosis?) Presented by DR. MAURICE J. COSTELLO.

Kaposi's Sarcoma. Presented by DR. WILBERT SACHS.

Black Hairy Tongue. Presented by DR. WILBERT SACHS.

Chromoblastomycosis Occurring in New York City. Presented by DR. MAURICE J. COSTELLO.

RHODE ISLAND DERMATOLOGICAL SOCIETY

Carl S. Sawyer, M.D., President
Bencel L. Schiff, M.D., Secretary
Nov. 12, 1957

Granulomatosis Disciformis of Miescher. Presented by Dr. Francesco Ronchese.

A husky 42-year-old instructor in auto driving was seen in 1953 with phlebitis on his left thigh. Subsequently he developed three round eczematoid patches, measuring 1 by 1 cm. in diameter, on his legs. He moved to San Francisco a few months later, and he claims that the patches enlarged, increased in number, and became uncomfortable. Dr. Winer, in 1955, made a diagnosis of granulomatosis disciformis progressiva et atrophica of Miescher. A biopsy specimen of one of the lesions showed a histological picture similar to erythema induratum. The tuberculin test at 1:1000 dilution was negative. Coccidiomycin test was negative. The trichophytin test was strongly positive. No organisms could be cultivated from lesions. Various antibiotics, including Terramycin, intramuscularly administered Combiotic, staphylococcic vaccine, and hydrocortisone, had no effect.

His family history revealed that his mother had been diabetic in her last four years of life.

At present the patient appears, as in 1953, in excellent general health. The patches now number eight; all but one are disk- or discus-shaped and have a raised but not firm border, somewhat resembling superficial basal-cell epithelioma. The border is erythematous and scaly and is studded with tiny serum-oozing holes. They measure 4 cm. in diameter. The central portion shows a soft whitish wrinkly scar.

Sections studied by Mescon are reported as follows: "Granulomatous infiltrate of the lower dermis and subcutaneous tissue. In some foci it is composed of varying numbers of lymphocytes and plasma cells, in other foci there are numerous foreign body and/or Langhan's type of multinucleated giant cells with some suggestion of epithelioid cells but without an unequivocal picture of tubercle formation. Negative guinea pig inoculation, negative culture for tubercle bacilli and negative acid-fast would tend to make unlikely tuberculosis and leprosy. A negative PAS stain and negative culture for fungi do not permit a diagnosis of a deep mycosis. Atypical erythema nodosum and erythema induratum and suppurative or nonsuppurative panniculitis could give this histologic picture. The marked degree of foreign body reaction and the absence of noninflammatory necrobiotic areas tend to exclude necrobiosis."

General physical examination did not reveal any abnormality. Sugar-tolerance test was negative. Spinal fluid, urine, blood, sedimentation rate, and icterus index were all within normal limits.

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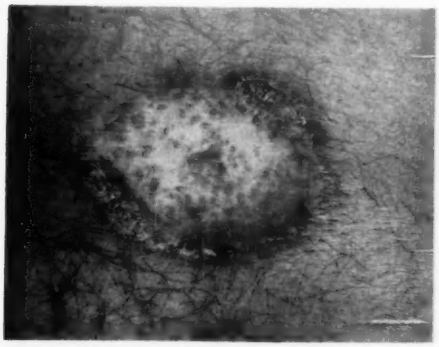
Case of granulomatosis disciformis progressiva et atrophica of Miescher.



Discussion

Dr. Bencel L. Schiff: Some years ago all these cases would have been considered necrobiosis lipoidica diabeticorum. However, Miescher and others leave no doubt that granulomatosis disciformis chronica et progressiva is an entity. The mechanism producing this dermatosis is still unknown. I agree with the diagnosis presented. The histology, as interpreted by Dr. Mescon, favors such a diagnosis. I suggest that the lesion be painted with thorium X and that the patient be given a trial of chloroquine orally.

Dr. Arthur B. Kern: I agree with the diagnosis of granulomatosis disciformis chronica et progressiva although the clinical picture was also suggestive of a deep mycosis, such as blastomycosis. Previous investigators have noted the histologic similarity of granulomatosis disciformis to erythema induratum. The histologic studies in this case also suggest the possibility that we might be dealing with an atypical erythema induratum. I would therefore recommend a trial of isoniazid or if this should fail a course of some of the other antituberculous medicaments.

Dr. Francesco Ronchese: In other cases of this disorder presented before dermatological societies, one of the points discussed was the similarity to necrobiosis lipoidica. The characteristic yellowish waxy shiny telangectatic appearance and firm fixed-to-the-underlying-structures consistency

of necrobiosis lipoidica are absent in this case. Granulomatosis en plaques could be just as good a term. We are used to unknown etiologies in dermatology and must be resigned to morphologic terms until the etiology is found. The lesions are certainly chronic, progressive, disk-like, and superficial. In the absence of proof that the dermatosis is a manifestation of an internal disease, it would be worth while to try surgical excision and graft, as are done for early lesions of lupus vulgaris.

Lupus Vulgaris. Presented by DR. FRANCESCO RONCHESE.

Lichen Planus. Presented by DR. CARL S. SAWYER.

Vasculitis. Presented by DR. MALCOLM WINKLER.

Pemphigus Erythematodes. Presented by DR. ARTHUR B. KERN.

Dermatomyositis. Presented by DR. ARTHUR B. KERN.

Lichen Planus Pilaris. Presented by DR. MALCOLM WINKLER.

The New, Newer, and Newest

Does it seem to you that the meetings you miss turn out to have been the "best yet?" Circumstances prevented my attending the meeting of the American Dermatological Association at Sun Valley, Idaho, this year, and, sure enough, word has it that the papers were "interesting," the discussions "excellent," the weather "perfect," the company "congenial," and the social activities "delightful." The new officers for 1958 are J. Lamar Callaway, President; Anthony Cipollaro, Vice-President, and Wiley Sams, Secretary.

Word has it that both meetings this year were well worth attending. The new officers of the A. M. A. Section are Clarence S. Livingood, Chairman; Rudolph Ruedeman, Vice-Chairman; Edward P. Cawley; Harry Arnold Jr., Assistant Secretary; Winfred Showman, Delegate to the House of Delegates; Maurice J. Costello, Assistant Delegate, and Stanley Huff, Representative to Scientific Exhibit. Poor Stanley Huff—no assistant!

The rash of drug eruptions lately reminds us of this admonition from a sound and seasoned Attending man during internship days. He was discussing new drugs and counseled, "for the first year give it to animals, the second year to your enemies, the third year to your patients, and the fourth year take it yourself if it is absolutely unavoidable."

We asked recently about the fate of spleen liquid which was so popular a decade or two ago. Comes the answer from Leonard Grayson, of Quincy, Ill.: "Spleen liquid is no longer available because the S. A. P. S.* have been buying all available spleens in America. The S. A. P. S. is now on their fourth Five-Year Plan of research of the effect of spleen liquid on the altered ego as a stimulant of ano-genital pruritus. It is the opinion of this eminent group that spleen liquid has something (this something we hope to identify during the next Five-Year Plan) that appears to stimulate the organs in some of the test animals in a way as to cause psychic effect when using certain doses in the bases.

Have Slides Will Travel Department

Kurt Wiener, of Milwaukee, whose hobby for years has been to travel round the world photographing the paintings of the Masters, will show a few of his 40,000 colored transparencies to the members of the Chicago Dermatological Society on the occasion of the Pusey dinner meeting on Oct. 15—and

I, too, have been assembling slides for Chattanooga, Sept. 30, for the Tennessee Valley Medical Assembly to discuss hand eczema; in Chicago, Oct. 27, for the Chicago Medical Society Post-graduate Course to discuss "Allergic Eczema," an assigned title; and in Houston, Oct. 24, for the University of Texas Postgraduate School of Medicine to discuss Dermatologic Problems of the Elderly, a subject of something more than academic interest to me.

In Los Angeles, the gracious Floralou Kettenbach has been elected President of the Los Angeles Dermatological Society; Jerome K. Fisher, Secretary. In Texas, Dr. Porter Brown was awarded the Gold Headed Cane by his colleagues, a signal honor. Dr. Brown is not a dermatologist, but a good friend of our colleagues in Texas, who credit him with the high place enjoyed by dermatology in Cancer Society relations. In Chicago, 16 physicians met to celebrate a 45th anniversary of their graduation from Rush Medical College—memories were refreshed when James Herbert Mitchell sprang a surprise and showed 20 sketches of professors and fellow students drawn four decades ago with "pencils, burnt matches, and what have you."

And Mitchell tells of a patient with alopecia totalis who was cautioned by his physician not to wear a wig for fear it would make his conditions worse.

HR

* Splenic Association of Physicians and Surgeons Signed, L.D., M.D., CROC. What is CROC?

Announcements

Papers for Section on Dermatology, American Medical Association.—Dermatologists and other physicians who may be interested in presenting a scientific paper before the Section on Dermatology of the American Medical Association, which meets in Atlantic City in June, 1959, are invited to submit the title and a 100- to 150-word abstract of the proposed paper for consideration by the Program Committee. Abstracts should be sent to the Secretary of the Section on Dermatology, Dr. Edward P. Cawley, University of Virginia Hospital, Charlottesville, Va. The deadline for submission of abstracts is Dec. 1, 1958.

Labeling Hazardous Substances in Packaged Chemicals.—The growing demand for uniform legislation to require precautionary labeling of all chemical products which are not now so regulated was discussed at the first legislative conference, held on May 9, 1958, at the American Medical Association headquarters. Speaking to government, industry, and medical represenatives from approximately 40 national organizations, members of the A. M. A. Committee on Toxicology discussed the "Uniform Hazardous Substances Act" and compared it with other tentative legislation which has been proposed.

Attention was focused on the general nature of the problem, as seen by the medical profession, public health officials, and the public and by remarks from a pediatrics representative and officials of the American Public Health Association and the National Safety Council. The principles which the Committee employed in formulating the provisions of a model law for labeling all types of hazardous substances were next reviewed. A comparison of the model bill with other tentative legislative proposals followed.

An industry-wide law conference was held on July 25, 1958, under the sponsorship of the Committee on Toxicology. The second meeting discussed proposed legislation requiring the declaration of hazardous ingredients and warning statements on the label and in the accompanying literature of household, commercial, and industrial packaged chemicals. Over 100 organizations, including representatives of trade associations, toxicity testing laboratories, chemical trade unions, and other interested groups, were invited to participate.

This was the second of several meetings which will be held to discuss proposals for local and federal regulations to close the gap in label legislation. A Committee survey showed a sketchy, nonuniform, and generally inadequate pattern of labeling regulations at the state and national level. Ninety per cent of the states lacked requirements for precautionary labeling of commercial as well as household chemical products. These meetings were held to bring about a clearer understanding of what the model bill is intended to cover and the benefits to be derived from such legislation.

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Books

Pharmacology in Medicine: A Collaborative Textbook. By Victor A. Drill, Ph.D., M.D. Price, $19.50. Pp. 1243. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1958.

This is a monumental reference book which represents the collaborative efforts of a number of pharmacologist-teachers. It deals with drugs currently used in practice with emphasis on their mechanism of action, effects within the body, therapeutic value and available forms. All material conforms with the United States Pharmacopoeia, the National Formulary, and New and Non-Official Drugs. The chapter devoted to the skin and mucous membranes, written by Eldon M. Boyd, Professor of Pharmacology at Queens University, considers adsorbents, demulcents, emollients, astringents, local irritants, melanizing, and demelanizing agents. Other drugs of interest to dermatologists thread through the entire book as, for instance, local anesthetics, vitamins, chemotherapeutic etc.—and there is an excellent section on prescription writing. It is a fine book to have on hand for ready reference, should one want to know what he is doing with the drugs that he prescribes.

The Practice of Infectious Diseases. By Louis Weinstein, Ph.D., M.D. Price, $8.50. Pp. 501. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1958.

Despite antibiotics, "the field of infections is expanding and not contracting." The author thought it timely to undertake to review the subject with emphasis on the practical aspects of the subject. After considering the principles of diagnosis, treatment and prevention, infections of special organs and systems are considered with two chapters devoted specifically to the skin. Dermatologic problems crop up in almost all the chapters, however. In general the book, written specifically for the general practitioner, covers the subject well and should prove useful.

The Healing of Wounds. By Martin B. Williamson, Ph.D. Price, $7.00. Pp. 202. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1957.

In recent years the healing of wounds has come to be studied both on the biological and molecular levels. A large amount of biochemical information has accumulated, some of it representing divergent viewpoints. To help bring them together, a symposium was held, and this book is a collection of 10 papers read at this symposium. The role of the ground substance, proteins, Vitamin C, hormonal influences, collagen, sulfur compounds and various clinical aspects are covered fully. The material and writing are uniformly excellent. The collection comprises a significant contribution to an important subject.

Der Lungenboeck im Röntgenbild. By Prof. Dr. K. Wurm, Prof. Dr. H. Reindell, and Prof. Dr. L. Heilmeyer. Price, DM 78. Pp. 220, with 214 illustrations. Georg Thieme, Herdweg 63, (14a) Stuttgart, Germany, 1958.

This book is essentially an x-ray atlas of the lungs in sarcoidosis or Besnier-Boeck-Schaumann's disease. Sixty-three cases are reported in some detail, with x-ray photographs taken at intervals in many of them. In addition, there are x-ray films of the lungs in a number of diseases which require consideration in differential diagnosis, such as tuberculosis, lymphogranulomatosis, lymphatic leukemia, lymphosarcoma, carcinoma, pulmonary sclerosis, and silicosis. The x-ray photographs are very well reproduced and give an excellent picture of the disease as it affects the lungs. The book should be of interest to the dermatologist seeking to increase his knowledge of the generalized lesions of sarcoidosis.

The Parasitic Fungi of Man. By Petr Frágner. Price, not given. Pp. 253, with 153 photographs and 27 sketches. The Czechoslovakian Academy of Science, Vodičkova 40, Prague II, 1958.

The author of this book is a scientist who, during the 13 years of his mycological studies, has had close contact with physicians and medical laboratories. In the first section of his work, the author describes the basic elements of mycological morphology, Cejp's system of the classification of fungi, and an outline of important mycological laboratory techniques. In the main part of the book, he deals with the special mycology of the various organisms found in man,

their position in the system of botanical mycology, their microscopic appearance and cultural behavior, and, very briefly, their clinical significance.

It is explained that inasmuch as there is a difference between the botanical and medical approaches to mycology great confusion has existed, resulting in a "tragic abundance" of synonyms. The author has made it his task to coordinate both views. He avoids lengthy academic discussions and limits himself to simple statements of facts, which enhances the clarity of his work. Although the clinical aspects of mycology are treated intentionally in an extremely cursory and, at times, obsolete manner, the dermatologist will be able to use this manual in his mycological work to great advantage. The German translation of the Czech original is excellent and easy to read. An extensive bibliography of the important international literature and numerous illustrations further increase the value of this work.

General Diagnosis and Therapy of Skin Diseases: An Introduction to Dermatology for Students and Physicians. By Hermann Werner Siemens, M.D. Translated from German edition by Kurt Wiener, M.D. Price $10.00. Pp. 324, with 375 illustrations. The University of Chicago Press, 5750 Ellis Ave., Chicago 37, 1958.

This extraordinary book, though modest in size and price, clearly belongs among dermatology's classic great books. Dr. Wiener and The University of Chicago Press have done a great service to English-speaking medical students, physicians, and dermatologists by skillfully translating and reproducing with technical excellence Professor Siemens' remarkable volume, the German edition of which first appeared in 1952.

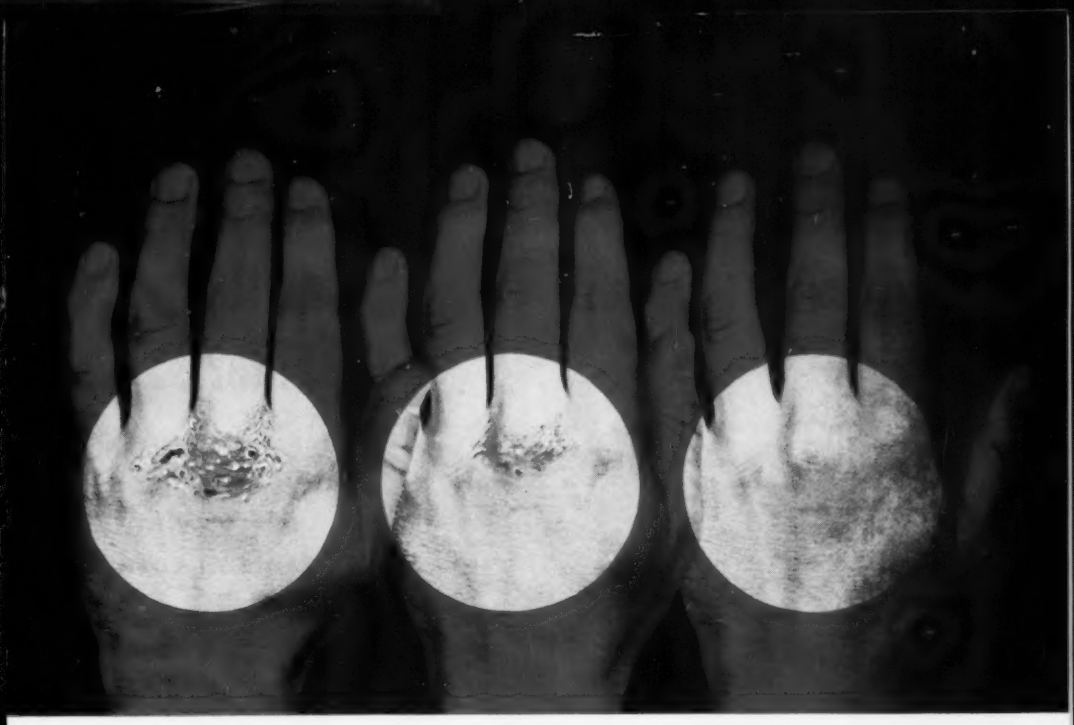
In this book the fundamental principles of dermatologic diagnosis and therapy are exposed under the critical glare of disciplined scientific analysis in detailed yet succint fashion and with unmatched clarity and precision. Better than any other book, this volume portrays the characteristics which distinguish dermatology from other medical specialties.

After a very concise review of cutaneous anatomy and histopathology, a major portion of the book is devoted to the morphology of lesions and eruptions. Lesions, as aptly stated by Darier, are the alphabet without which nobody can read the language of the skin. Professor Siemens presents this alphabet with fascinating clarity not only by means of his crisply precise text but also with the aid of hundreds of superb close-up photographs which truly represent the acme of modern black-and-white photographic art as applied to dermatology. The illustrations alone constitute a wonderful dermatologic atlas.

In brief chapters on systemic symptoms, subjective symptoms and history, and auxiliary diagnostic techniques, key points are selected and analyzed in a thoroughly sound and scientific manner. The pitfalls of fuzzy generalization in considering the roles of the psyche or of constitutional pathology in dermatologic disorders are appropriately exposed.

Most of the approximately one hundred pages on therapy concentrates on the scientific principles involved in topical treatment. Chief emphasis is placed on the crucial importance of maintaining a purely empirical rather than traditional approach to such therapy. The exact objective methods by which the efficacy of topical therapy can be assessed are also thoroughly discussed in a manner which captures the spirit of scientific curiosity and experiment. Throughout the entire volume the author's scholarly background, original thinking, and keen powers of observation and objective analysis are evident.

In short, this is a magnificent book about the very heart and core of dermatology, which trains the reader to see with the eyes and with the mind as well. It deserves careful reading not only by all who would approach the diagnosis or treatment of skin diseases but also by anyone seeking to learn about the scientific method as applied in the realm of the clinician.



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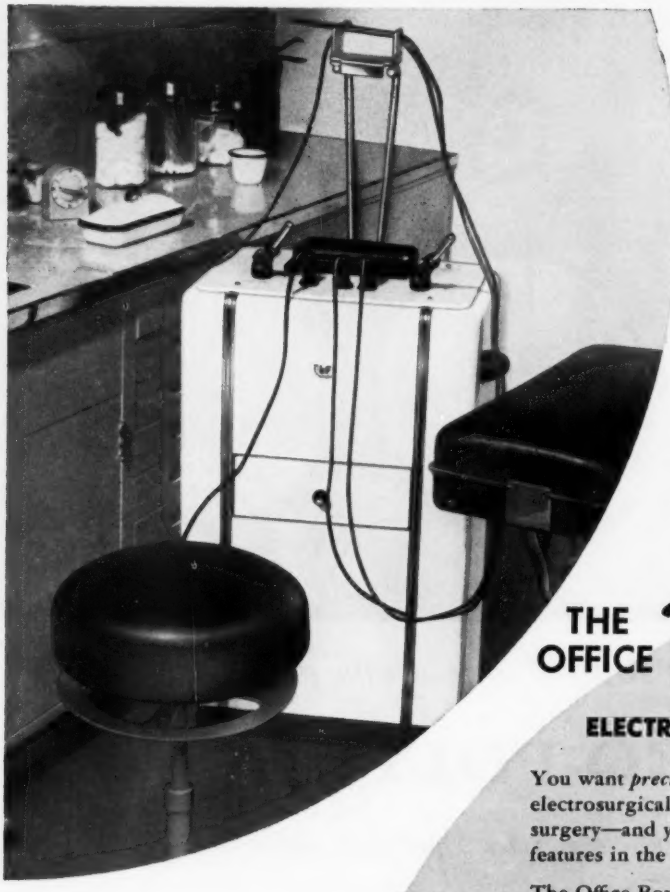

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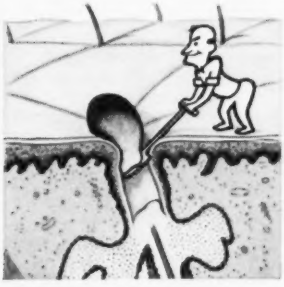

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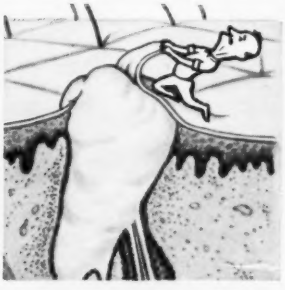

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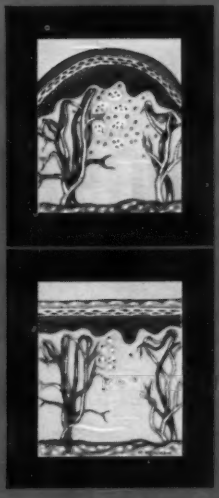

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Clyman, S. G.: Postgrad. Med. 21:309, 1957 • Bleiberg, J.: J. M. Soc. New Jersey 53:37, 1956 • Abrams, B. P., and Shaw, C.: Clin. Med. 3:839, 1956 • Bleiberg, J.: Am. Practitioner 8:1404, 1957

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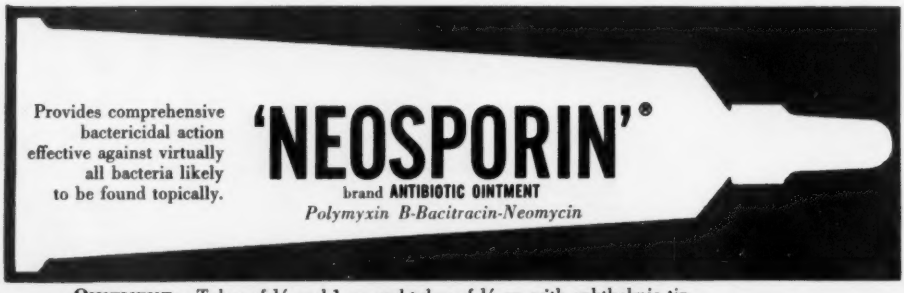
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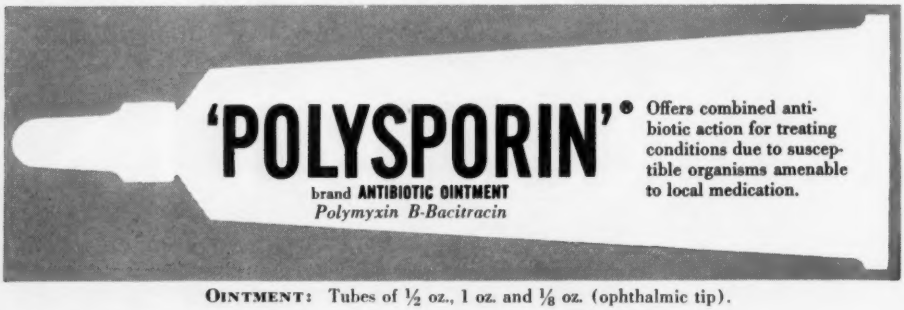
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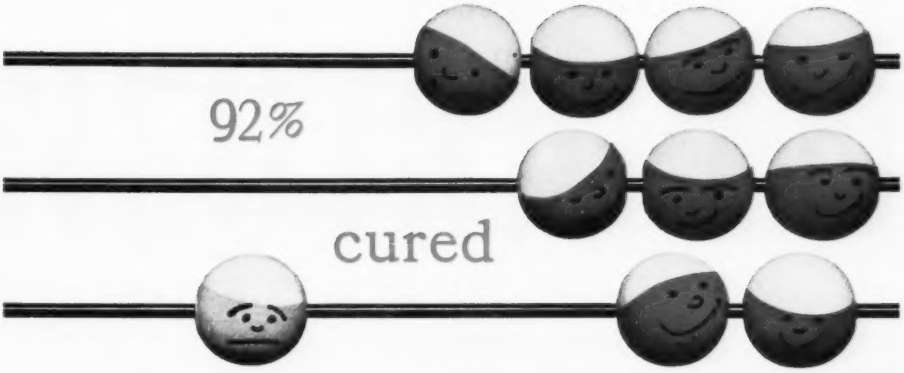

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1. Kuhn, B. H.: South. M. J. *49*:1122 (Oct.) 1956. • 2. Carrick, L.: J.A.M.A. *131*:1189 (Aug. 10) 1946. • 3. Hopkins, J. G., and others: A.M.A. Arch. Dermat. & Syph. *67*:479 (May) 1953. • 4. Sullivan, M., and Bereston, E. S.: J. Invest. Dermat. *19*:175 (Sept.) 1952.

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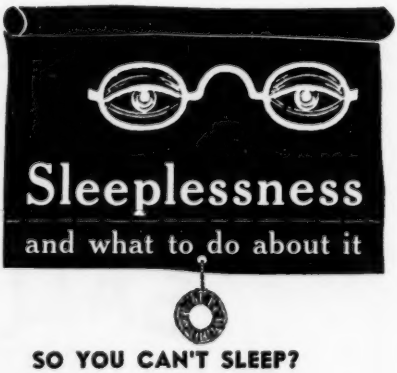

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references: (1) Becker, R. M.: New England J. Med. 254:952, 1956. (2) Chen, J. Y. F.; Bard, J. W., and Balsito, A. A., in Welch, H., and Marti-Ibanez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 321. (3) Zimmerman, M. C., in Welch, H., and Marti-Ibanez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 312. (4) Becker, R. M.: A New Concept in Treatment of Penicillin Reactions—Use of Penicillinase, paper presented at 106th Ann. Meet., A.M.A., New York, N. Y., June 3-7, 1957. (5) Becker, R. M., in Welch, H., and Marti-Ibanez, F.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 310. (6) Minno, A. M., and Davis, G. M.: J.A.M.A. 165:222, 1957. (7) Davis, G. M.: Discussion, Antibiotics Symposium, Washington, D. C., October 3, 1957. (8) Zimmerman, M. C.: Clin. Med. 5:305, 1958.

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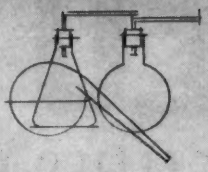

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1) Langs, R., and Strauss, M. B.: Paper read at AMA meeting, Section on Dermatology; San Francisco, June 25, 1958.

2) Langs, R., Strauss, M. B., and Fuchs, A. M.: Personal Communication.

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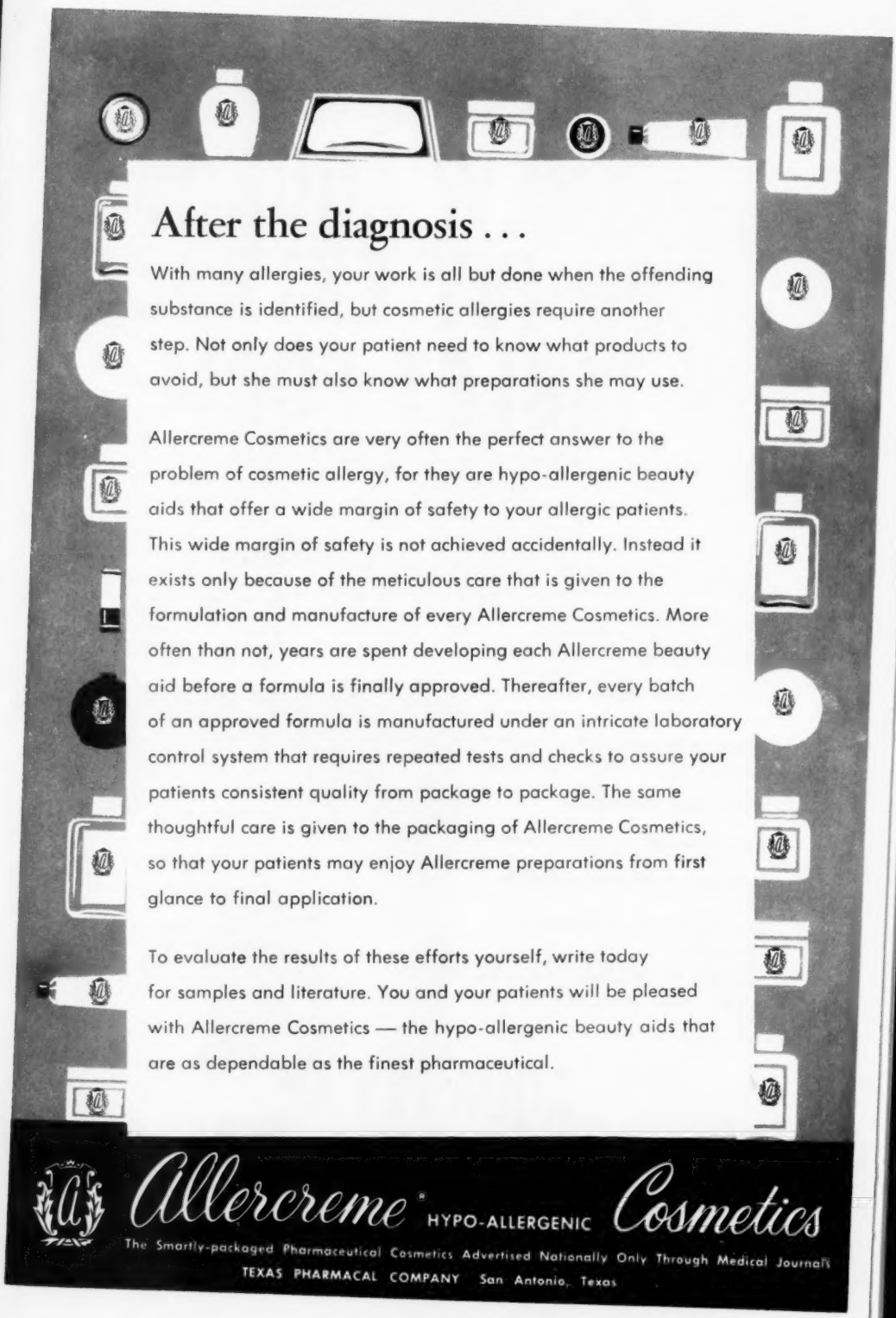
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TEXAS PHARMACAL COMPANY San Antonio, Texas

new study confirms
EFFECTIVENESS

101
out of
106

infected wounds
successfully
treated with

Panafil®
OINTMENT

"...offers the surgeon another...efficient approach to the treatment of infected surface lesions."*

A recent clinical study* has shown PANAFIL Ointment to be effective in 101 out of 106 suppurative wounds and ulcerations involving a variety of bacterial organisms. PANAFIL, the only local medication used in these cases, "...produced uniformly successful results." Systemic antibiotics were employed only in the more severe infections.

Three ingredients in PANAFIL produce a continuous *cleansing-protecting-healing* action in the wound:

Papain—effective debriding enzyme, gently and safely removes debris and slough detrimental to the healing process.

Urea—augments the cleansing action of papain, especially in encrusted lesions.

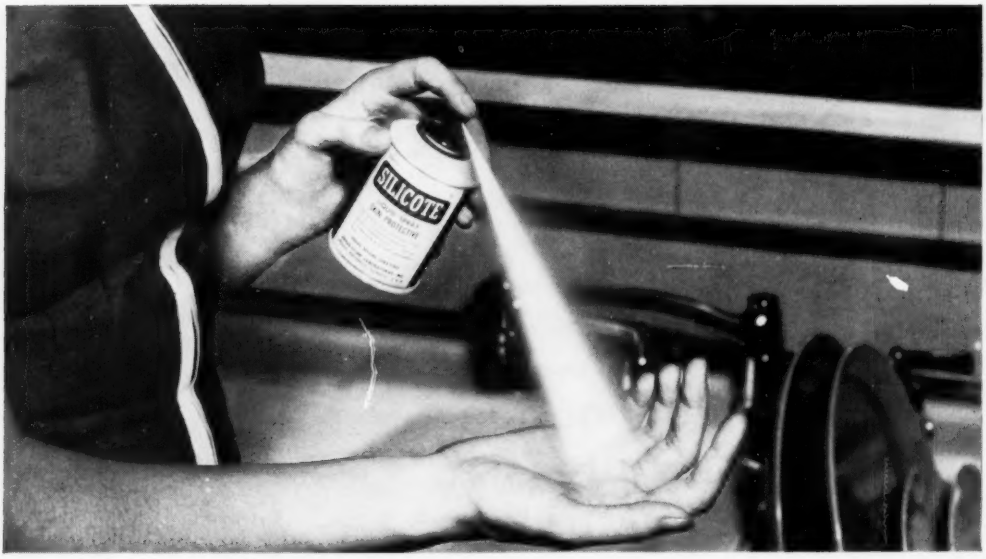
Chlorophyll derivatives—control inflammation, promote the growth of normal, healthy granulations.

PANAFIL Ointment contains papain 10%, urea U.S.P. 10%, and water-soluble chlorophyll derivatives 0.5% in a hydrophilic ointment base. Available in 1-ounce and 4-ounce tubes *on prescription only*.

*Miller, J. M.; Godfrey, G. C.; Ginsberg, M., and Papastrat, C. J., in Surgical Service, V. A. Hospital, Fort Howard, Maryland: Postgrad. Med. 22:609, 1957.

Rystan company • **Mount Vernon, N. Y.**

29488



Another First !

New SILICOTE® LIQUID SPRAY

PROTECTS SKIN AGAINST MANY IRRITANTS

Your patients can now spray on effective protection of the skin against common dry and aqueous irritants with new Silicote Liquid Spray.

Silicote Liquid Spray contains the unusually high concentration of 33 1/3% silicone (dimethicone) in a specially prepared liquid petrolatum base. It contains no water or water soluble ingredients. Silicote is the only preparation incorporating the silicones in petrolatum. Its formulation is similar to Silicote Ointment.

INDICATIONS:

Contact Dermatitis: Soaps, detergents, cosmetics.

Industrial Dermatoses: Acids, alkalies, foods, drugs, coolants, soluble cutting oils.

Surgical Drainage: Colostomy, ileostomy, draining fistulas and sinuses.

Hospital Skin Problems: Sheet burn, decubitus ulcers, incontinence.

Pediatric Skin Problems: Diaper rash, drooling, nasal drainage.

Chapping, Chafing, Intertrigo.

ADVANTAGES:

- Quick, easy application
- Prolonged, effective skin protection
- Assures patient cooperation
- Softens skin
- Non-tacky feeling
- Eliminates need for gloves
- Virtually nonocclusive, nonsensitizing, nontoxic

APPLICATION: Cleanse area. Shake dispenser before spraying and hold 10" from skin. **Hands:** Spray and rub in with hand-washing motion. Remove excess with cloth. Apply before each exposure to irritating substance. **Other Areas:** Apply routinely with each change of diaper or dressing. **Contraindications:** Do not use on weeping or infected areas.

SUPPLIED: 3 oz. aerosol containers. (Also available, Silicote Ointment.)

By the Originators of Aerosol Medications

SEND FOR LITERATURE

ARNAR-STONE LABORATORIES, INC.

SILICOTE

LIQUID SPRAY SKIN PROTECTIVE

225 E. PROSPECT AVE., MT. PROSPECT, ILL.

New

LIQUIMAT

A new tinted lotion containing 5% precipitated sulfur for the local treatment of acne. Resorcin, calamine, phenol, menthol, camphor, betanapthol and coal tar solution may be added. To individualize your prescription further, the three shades may be interblended. In 3 ounce plastic bottles.

a fine, dependable, flexible line for the treatment of . . .

acne

SULFORCIN LOTION

contains 5% dispersible sulfur and 3% resorcinol monoacetate in a colloid-processed base of citrus pectin. Sulforcin Lotion dries rapidly, holding sulfur securely to the skin. Non-sticky, non-greasy, non-staining.

SULFORCIN CREAM

contains 5% dispersible sulfur and 3% resorcinol monoacetate in a water soluble vanishing cream type base. Lubricating and washable, Sulforcin Cream is especially suitable for application to large areas, and where dryness exists.

SULFORCIN BASES

a greaseless cream type make-up base supplied in 2* strengths and 3 shades which enable you to prescribe more individually for your patients' needs. Sulforcin Base helps conceal blemishes and is an excellent make-up foundation.

SEBA-NIL

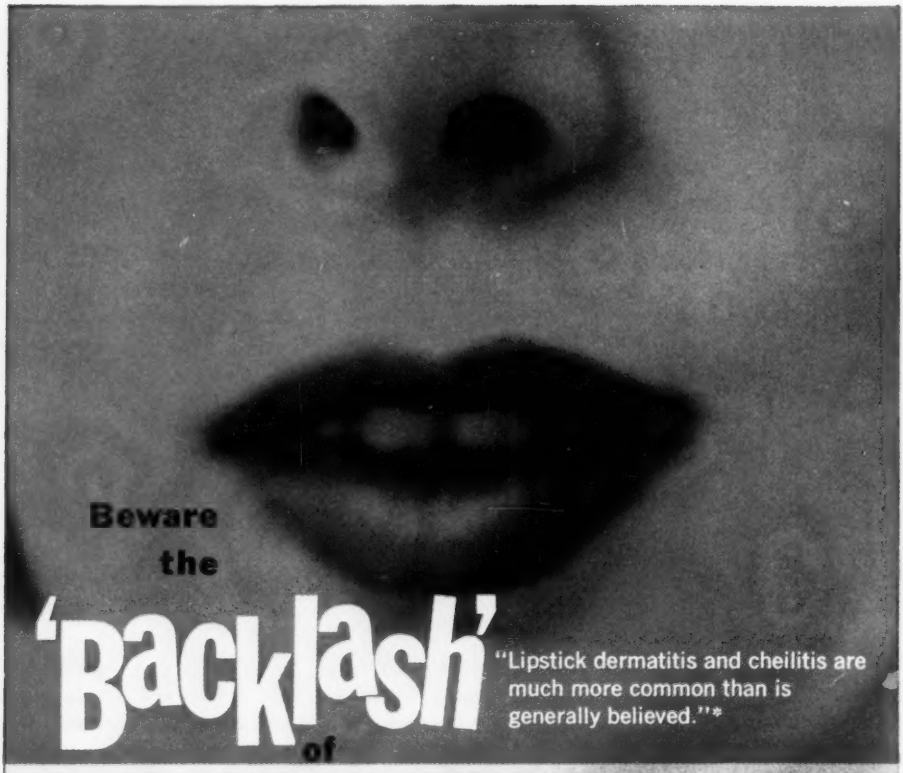
Clinical studies prove conclusively that very oily skins respond more rapidly to acne therapy when cleansed with Seba-Nil rather than soap and water. Seba-Nil contains organic solvents and a mild, non-ionic detergent which make it more efficient than soap and water in preparing oily skin for medication.

**Also available: Plain Resorin-free Sulforcin Base, containing 2½% sulfur only.*

For detailed information and samples, write . . .

TEXAS PHARMACAL COMPANY

San Antonio, Texas



Dermatoses resulting from sensitivity to a variety of lipstick ingredients can be avoided by using MARCELLE Lipsticks — another reason to remember and suggest MARCELLE® HYPOALLERGENIC COSMETICS for the patient with a cosmetic allergy or sensitivity.

MARCELLE Lipsticks — available in a full range of colors — are offered in different formulas to eliminate common sensitizers, and to avoid perfumes and the bromofluoresceins. The MARCELLE Lipstick Testing Kit, providing 14 different formulations, enables you to help your patient select a lipstick best suited to her case.

Marcelle COSMETICS, INC.
CHICAGO 47, ILLINOIS

a subsidiary of
Borden's
BORDEN'S Pharmaceutical Division

*Zakon, S. J., et al.: Arch. Dermat. & Syph. 56:499, 1947; abstracted in Birmingham, D. J., and Campbell, P. C., Jr.: Occupational and Related Dermatoses, U. S. Public Health Service Publication No. 364, 1954.

NOW...an advanced ACTH

SIGNIFICANTLY IMPROVED

CORTROPHIN®-ZINC

(Corticotropin-Alpha Zinc Hydroxide)

A unique electrolytic process* of manufacture gives a fine, easily resuspended aqueous suspension of Cortrophin-Zinc with these therapeutic advantages:

★ **VIRTUALLY PAINLESS** . . . . Unsurpassed patient acceptance.

★ **HIGH PURITY** . . . . . Virtually pure ACTH with fewer mg. of foreign protein per injection.

★ **RAPID ACTION** . . . . . New form stimulates peak adrenal output within two hours.

★ **LONG ACTION** . . . . . Provides ACTH activity for several days.

★ **ECONOMICAL** . . . . . Lower total ACTH dosage and fewer injections required.

Cortrophin-Zinc is indicated in the treatment of more than 100 diseases, including rheumatoid arthritis, bronchial asthma, allergies and hypersensitivities, bursitis, serum sickness, conjunctivitis and other eye diseases, ulcerative colitis, atopic dermatitis and other skin diseases.

★ **ASK YOUR ORGANON REPRESENTATIVE OR WRITE FOR CLINICAL AND EXPERIMENTAL REPORTS SUBSTANTIATING THESE CLAIMS.**

SUPPLIED: 5-cc vials containing 40 and 20 U.S.P. units of corticotropin per cc; 1-cc ampuls containing 40 and 20 U.S.P. units of corticotropin, with sterile disposable syringes.

Pat. Pending
Available in other countries as Cortrophine-Z.

Organon inc. ORANGE, N. J.

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FOR YOUR EVERY-DAY SKIN PROBLEMS

for standard colloid bath therapy . . .

AVEENO* *soothing* Colloid Baths

- *time-tested*
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*AVEENO® Colloidal Oatmeal is available in 18 oz. and 4 lb. boxes

where extra emolliency is desired . . .

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Colloidal Emollient Baths

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AVEENO® "OILATED" (super-oiled colloidal oatmeal concentrate) is available in 10 oz. hermetically sealed cans.

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A new highly effective

SHALE TAR

Metashal®

Solubilized Colorado Shale Tar, Stiefel

"especially impressive...in atopic dermatitis of all ages and stages"[4]

Compatible with all standard dermatologic drugs, such as hydrocortisone, salicylic acid, menthol and iodochlorhydroxyquin.

METASHAL, a Colorado shale tar that is different from conventional coal tars, has been found to be "especially impressive . . . in atopic dermatitis of all ages and stages."[4] Another investigator has reported that it "seems to be particularly effective in many cases of atopic dermatitis" in infants and children.[1]

Confirming previous studies,[2] a report of 414 cases of atopic and contact dermatitis and other skin diseases showed that shale tar therapy resulted in a favorable response in 96.3%.[3]

In another report of 365 cases from several different investigators, "excellent" or "very good" results were obtained with METASHAL in 93.75% of atopic dermatitis cases in infants and children, and fair to excellent results in 94.4% of atopic dermatitis cases in juveniles and adults.[4]

SUPPLY: METASHAL OINTMENT, containing 8.7% shale tar, for heavier, lichenified, subacute and chronic lesions. METASHAL LOTION, containing 18% shale tar in zinc oxide-talc shake lotion, for moist, more acute phases. Available only on your prescription.

SEND FOR SAMPLES.

REFERENCES: 1. Howell, C. M.: N. Carolina M.J. 18:322, 1957. 2. Brandt, R., and Dexter, H.: J. Invest. Dermat. 15:163, 1950. 3. Brandt, R., and Dexter, H.: Ibid. 19:409, 1952. 4. Brandt, R., and Szolomejer, W.: A.M.A. Arch. Dermat. 76:241, 1957.

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88% CURE RATE

in a wide variety of PYODERMAS

BACIMYCIN®

[BACITRACIN-NEOMYCIN] OINTMENT

a first choice for dual antibiotic therapy

In a recent study[1] of 53 patients with various types of pyodermas, the use of BACIMYCIN Ointment "... resulted in a cure rate of 88%...." Impetigo, infectious eczematoid dermatitis, atopic eczema, secondary infections superimposed on dermatitis venenata, and folliculitis were among the common skin infections that showed marked improvement with BACIMYCIN therapy.

BACIMYCIN rarely produces sensitization or primary irritation.

Supplied in ½ oz. tubes for prescriptions; in 100 gm. jars for hospital use; in ⅛ oz. tubes for ophthalmic use. Also supplied as BACIMYCIN with Hydrocortisone, ⅛ oz. tube with applicator tip.

Literature and samples on request.

1. Greenhouse, J. M., and Ryle, W. C.: A.M.A. Arch. Dermat. & Syph. 69:366 (March) 1954.

Walker LABORATORIES, INC. MOUNT VERNON, NEW YORK

NEW non-inflammable Gebauer's FLURO-ETHYL

(FLUORINATED-HYDROCARBON)

FLURO-ETHYL is a solution of Ethyl-Chloride and Dichlorotetrafluoro-ethane which has been demonstrated to be useful as a topical refrigerant for use in plastic surgical skin planing and as an agent to produce local anesthesia for minor surgical procedures. It contains 75% Dichlorotetrafluoro-ethane and 25% Ethyl-Chloride, and when applied topically to the skin, produces rapid refrigeration and anesthesia to the desired depths of the skin.

CLINICAL USES:

Plastic Surgical Skin Planing: In the refrigeration dermabrasion technique GEBAUER'S FLURO-ETHYL is a refrigerant of choice because it eliminates the necessity of a blower. The mixture is non-inflammable and it produces rapid anesthesia and refrigeration to the required depths of the skin. In addition, the mixture does not give the patient a feeling of suffocation if inhaled. The area to be refrigerated can easily be controlled to the desired limits.

Although this preparation is specially designed for plastic surgical skin planing, it can also be used as a local anesthetic for minor procedures such as incision of furuncles, electrocautery to small cutaneous tags, flat warts, and nevi, or the alleviation of needle pain during hypodermic injection.

HOW IT'S USED

When using GEBAUER'S FLURO-ETHYL, holding same in an inverted position, the solution is then delivered onto the skin in the form of a fine, mist-like spray, producing a degree of anesthesia by refrigeration adequate for skin planing without the use of an air blower. To obtain best results place container in cooler before using.

MANUFACTURED BY

THE GEBAUER CHEMICAL CO.

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